Medtronic CoreValve® U.S. Pivotal Trial

(High Risk Surgical Patients)

Clinical Investigational Plan

Version 14.0

February 10, 2014

Sponsor:
Medtronic, Inc.
Clinical Research
Mailstop: MVS66
Mounds View South
8200 Coral Sea St NE
Mounds View, MN 55112

Trial Title:	Medtronic CoreValve® U.S. Pivotal Trial
IDE No.	G100012
CIP No.	MCV-US-2009-01 (High Risk Surgical)
Trial Oversight:	Eric Vang Clinical Research Director Medtronic CardioVascular Phone: (763) 514.9751 Email: eric.vang@medtronic.com
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1. SYNOPSIS

Title of Trial:	Medtronic CoreValve® U.S. Pivotal Trial
Title of Protocol:	Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)
Name of Product:	Medtronic CoreValve® System (MCS)
Purpose:	To evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.
Design:	Subjects will be randomized on a 1:1 basis to either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or to surgical aortic valve replacement (SAVR).
Primary Objective:	The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS) as measured by all-cause mortality rates at 12 months is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.
Primary Endpoint:	All-cause mortality at 12 months.
Secondary Endpoints:	The following secondary endpoints will be compared between MCS TAVI and SAVR subject cohorts: 1. Major Adverse Cardiovascular and Cerebrovascular Event (MACCE)-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years. MACCE is defined as a composite of: • all-cause death • myocardial infarction (MI) • all stroke, and • reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve) 2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

Secondary Endpoints (Continued):	3. Major Adverse Events (MAE) at 30 days, 6 months,12 months and annually thereafter up to 5 years. 4. Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years. 5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years. 6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months. 7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up. 8. Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures: • Kansas City Cardiomyopathy Questionnaire (KCCQ) • SF-12, and • EuroQoL 9. Echocardiographic assessment of prosthetic valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures: • transvalvular mean gradient • effective orifice area • degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular) 10. Aortic valve disease hospitalization at 30 days, 6 months, 12 months and annually thereafter up to 5 years. 11. Cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually thereafter up to 5 years. 12. Strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually thereafter up to 5 years. 13. Index procedure related MAEs. 14. Length of index procedure hospital stay.

Secondary Endpoints (Continued):	The following secondary endpoints will be assessed for the MCS TAVI cohort subjects only: 15. Device success defined as follows: • successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system, • correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function), • Intended performance of the prosthetic valve[1] (aortic valve area > 1.2 cm^2 for 26, 29 and 31mm valves, ≥ 0.9 cm^2 for 23mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR) • Only one valve implanted in the proper anatomical location [1] assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge 16. Procedural success, defined as device success and absence of in-hospital MACCE. 17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
Principal Investigators:	Jeffrey J. Popma, M.D. – Interventional Cardiologist David H. Adams, M.D. – Cardiothoracic Surgeon
Trial Sites:	The trial will be conducted at up to 45 sites in the United States.
Sample Size:	790 (395 MCS TAVI & 395 SAVR) and up to 40 additional subjects enrolled with approximately 20 subjects randomized to TAVI and receiving a 23mm valve Non-ilio-femoral will be limited to no more than 30% (249) of the 830 randomized subjects.
Patient Population:	Subjects with symptomatic severe aortic stenosis (AS), necessitating aortic valve replacement whose predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.
Inclusion Criteria:	1. Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree that predicted risk of operative mortality is ≥15% (and

Inclusion Criteria (Continued):	predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days. 2. Subject has senile degenerative aortic valve stenosis with: • mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterization (either resting or dobutamine stress), AND • an initial aortic valve area of ≤ 0.8 cm^2 (or aortic valve area index ≤ 0.5 cm^2/m^2) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization 3. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater. 4. The subject or the subject's legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site. 5. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
Exclusion Criteria:	**Clinical** 1. Evidence of an acute myocardial infarction ≤ 30 days before the intended treatment. 2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure including bare metal stents. Additionally, any drug eluting stents placed within 6 months prior to the index procedure. 3. Blood dyscrasias as defined: leukopenia (WBC < $1000mm^3$), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy. 4. Untreated clinically significant coronary artery disease requiring revascularization. 5. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support. 6. Need for emergency surgery for any reason.

Exclusion Criteria (Continued):	7. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram. 8. Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA). 9. End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min. 10. Active GI bleeding within the past 3 months. 11. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated: • aspirin • heparin (HIT/HITTS) • nitinol (titanium or nickel) • ticlopidine and clopidogrel • contrast media 12. Ongoing sepsis, including active endocarditis. 13. Subject refuses a blood transfusion. 14. Life expectancy < 12 months due to associated non-cardiac co-morbid conditions. 15. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent. 16. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits). 17. Currently participating in an investigational drug or another device trial. 18. Symptomatic carotid or vertebral artery disease. 19. Subject has been offered surgical aortic valve replacement but declined. **Anatomical** 20. Native aortic annulus size < 18 mm or > 29 mm per the baseline diagnostic imaging. 21. Pre-existing prosthetic heart valve in any position. 22. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)). 23. Moderate to severe (3-4+) or severe (4+) mitral or

<table>
<tr>
<td>Exclusion Criteria (Continued):</td>
<td>
severe (4+) tricuspid regurgitation.
24. Moderate to severe mitral stenosis.
25. Hypertrophic obstructive cardiomyopathy.
26. New or untreated echocardiographic evidence of intracardiac mass, thrombus or vegetation.
27. Severe basal septal hypertrophy with an outflow gradient.
28. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access).
29. Ascending aorta that exceeds the maximum diameter for any given native aortic annulus size (see table below)
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<tr><th>Aortic Annulus Diameter</th><th>Ascending Aorta Diameter</th></tr>
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<tr><td>27 mm – 29 mm</td><td>>43 mm</td></tr>
</table>
30. Congenital bicuspid or unicuspid valve verified by echocardiography.
31. Sinus of valsalva anatomy that would prevent adequate coronary perfusion
Vascular
32. Transarterial access not able to accommodate an 18Fr sheath.
</td>
</tr>
<tr><td>Enrollment Phase:</td><td>The enrollment phase is expected to last 20 months.</td></tr>
<tr><td>Follow-up Evaluations:</td><td>Subjects will be followed through 5 years with assessments at 30 days, 6 months, and 12 months as well as 2, 3, 4 and 5 years post MCS TAVI or post SAVR.</td></tr>
</table>

2. PURPOSE

2.1 Background

The management of heart disease in the elderly has been affected by the dramatic increase in life expectancy. With the number of persons over age 80 expected to increase to approximately 25 million by the year 2050[i], degenerative heart disease is likely to become an increasing problem. Calcific or degenerative aortic valve disease is considered the most common valvular lesion among elderly subjects[ii]. Aortic stenosis (AS) causes left ventricular outflow obstruction in adults, with severe AS defined as a combination of echocardiographic parameters: an aortic jet velocity >4 m/s, a mean gradient >40 mmHg, and a valve area <1.0 cm^2, according to the ACC/AHA guidelines for the management of valvular heart disease[iii]. Severe aortic stenosis is also considered to be present if the valve area index is < 0.6 cm^2/m^2. However, in patients with severe AS who also have a low cardiac output state, the aortic jet velocity and mean gradient may be lower, a condition known as low-gradient stenosis. Subjects with AS can remain asymptomatic for a prolonged period, although once symptoms develop, prompt intervention is required[iii]. The classic symptoms associated with AS typically occur with exertion and include heart failure, syncope, and angina. Surgical replacement of the aortic valve is the only effective treatment for severe AS currently approved in the United States.

For those subjects ineligible for open-heart surgery, however, therapeutic options include only the palliative measures of medical therapy or percutaneous aortic valvuloplasty. Percutaneous balloon aortic valvuloplasty (BAV) has been suggested as an alternative to aortic valve replacement in subjects with AS[iv] and can result in improved symptoms. However, the high incidence of residual or recurrent stenosis and serious complications have limited the utility of this technique in the elderly[v,vi,vii.] Subjects deemed too high risk to undergo aortic valve replacement (AVR) experience very high mortality rates, with average survival only two to three years[viii].

In order to identify “high-risk” subjects for mortality following AVR, a number of scoring systems have been developed. The Society of Thoracic Surgeons (STS) Predicted Risk of Mortality appears to be the most accurate score for predicting perioperative and long-term mortality and morbidity in subjects undergoing aortic valve replacement. Dewey and colleagues compared the mean and logistic Euro System for Cardiac Operative Risk Evaluation (EuroSCORE), the Society of Thoracic Surgeons (STS) risk score, and the Ambler Risk Score in 638 subjects who underwent isolated aortic valve replacement. Subjects at or above the 90th percentile of risk (8.38% for STS, 33.47% for logistic, 12% for additive, 14.3% for Ambler) were identified as “high-risk” subjects for aortic valve replacement. Long-term mortality, per high-risk group, was 64.1% in the STS Predicted Risk of Mortality, 45.3% in the logistic, 45.2% in the additive, and 40.2% in Ambler Risk Score, and logistic regression showed that the STS algorithm was the most sensitive in defining the subjects most at risk for long-term mortality[ix]. There are also potential risks associated with cardiopulmonary bypass in high-risk subjects,

and minimally invasive surgical approach has lessened but not eliminated these risks[x].

Moreover, there are subjects who are deemed non-surgical due to prohibitive medical and anatomical conditions including highly compromised respiratory disease, severe immunosuppressive diseases, “true” porcelain aorta, chest wall radiation or deformity and multiple previous interventions in the presence of advanced multi-system dysfunction. Most of these characteristics are not included in the STS or other risk assessment systems (often such subjects will score less than an STS of 10). Despite the limitations noted, subjects with severe aortic stenosis who are not candidates for aortic valve replacement may undergo balloon valvuloplasty as a palliative procedure[xi,xii,xiii]. In a series reported by Shareghi and colleagues, 80 consecutive subjects with symptomatic severe aortic stenosis underwent 104 balloon aortic valvuloplasty procedures and were followed for a mean of 3±2 years. Repeated valvuloplasty was needed in 15 subjects over the course of follow-up, including 5 balloon valvuloplasties in one subject. Nine percent of subjects had vascular complications. In-hospital, 1, 2- and 3-year mortality rates were 6%, 44%, 62% and 71%, respectively[xiii]. In another series reported by Sack and colleagues, BAV was performed in 75 subjects who were not candidates for surgical aortic valve replacement. Serious adverse events occurred in 17% of the BAV procedures. The mortality rates at 6 months and 12 months were 25% and 29%, respectively[xii]. Contemporary BAV has acceptable short- and mid-term results and can effectively be used for subjects deemed unsuitable surgical candidates and those at highest operative risk, such as subjects with cardiogenic shock, but these therapies should be considered only palliative in nature.

A more viable long-term solution for high or extreme risk subjects for AS may be the development of transcatheter aortic valve implant (TAVI), which would provide the benefit of valve replacement without the associated risks of open-heart surgery[xiv]. Recent advances in both percutaneous techniques and concurrent technological advances in the evolution of collapsible bioprosthetic aortic valves have led to cautious optimism about this emerging approach[xv,xvi].

Less invasive percutaneous aortic valve procedures have emerged[x,xvii]. Medtronic CoreValve® has developed the Medtronic CoreValve® System (MCS) which consists of a porcine pericardial bioprosthetic valve mounted and sutured in a self-expanding Nitinol frame. The bioprosthesis is housed in a collapsed position for percutaneous delivery via a catheter-based technique, and implanted within the diseased aortic valve. At the discretion of the participating physician (in accordance with the local standard of care), the procedure is performed utilizing local anesthesia (with or without conscious sedation) or under general anesthesia (with or without hemodynamic support or cardiac assistance).

The primary access site for the Medtronic CoreValve® System is the artery. The transfemoral approach has been reported in more than 15 published outcomes articles as of September 2010 representing more than 2500 procedures. In addition, the subclavian/axillary or direct aortic approaches have also been used as alternative access sites. The subclavian/axillary approach has been reported in nine published outcomes articles as of September 2010 representing more

than 100 procedures, and may represent up to 10% of implants at some implanting centers[xviii].

The purpose of this protocol is to evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. High risk surgical subjects will be randomized to receive either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or SAVR in a 1:1 ratio.

The primary endpoint is all cause mortality at 12 months. The assumption for 12 month mortality for the SAVR arm is an estimate based on 12-month mortality as reported in the surgical literature for high risk AVR (table below). The subjects enrolled in this study are expected to have a higher mortality than observed in the surgical literature, as subjects enrolled in the High Risk Surgical Cohort must have an expected *perioperative* mortality of 15% (based on Investigator-estimated mortality or STS score >10). The complete references to the studies used to estimate the rates for the BAV and AVR comparator arms can be found in Section 16.

Table 1. All-cause mortality rates of high risk population from published data.

Study	Year	N	Mortality at 12 months
Elayda et al.[xix]	1993	77	16%
Sundt et al.[xx]	2000	133	20%
Chiappini et al.[xxi]	2004	71	10%
Collart et al.[xxii]	2005	215	16%
Varadarajan et al.[xxiii]	2006	80	13%
Melby et al.[xxiv]	2007	105	18%

Currently, the average patient undergoing surgery is older and has a greater number of comorbities than the previously studied population. Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month all-cause mortality rate among high risk SAVR subjects in the current study will be 20%.

Sundt et al.[xx], Collart et al.[xxii], and Melby et al.[xxiv] reported MACCE rates at 30 days. From these studies, the MACCE (defined as a composite of all cause death, MI (Q-wave and non-Q-wave), emergent cardiac surgery, stroke, and reintervention) rate ranged from 15% to 31% with meta-analytic average of 20.1% (95% CI 16.5-23.8%). Thus, for the current study it is assumed that the expected MACCE rate at 30 days will be 20%.

2.2 Medtronic CoreValve® System and Intended Use

The Medtronic CoreValve® System is intended for use in subjects with severe symptomatic Aortic Stenosis (AS), necessitating aortic valve replacement whose

predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.

2.3 Primary Objective

The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS), as measured by all cause mortality rates at 12 months, is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.

3. TRIAL PROTOCOL

3.1 Ethics & Regulatory Compliance

3.1.1 Applicable Regulations

This trial will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the United States Food and Drug Administration (FDA) and local regulations where applicable, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

3.1.2 Institutional Review Board (IRB)

The trial will be conducted in accordance with 21 CFR 56 Institutional Review Boards. The trial protocol and consent must be approved by the responsible Institutional Review Board (IRB) at each investigational site. Trial activities must not commence prior to receipt of documentation of IRB approval by the site and Medtronic. The Investigator and trial staff must comply with the requirements of their IRB.

3.1.3 Ethical Conduct of the Trial

The trial will be conducted in accordance with the design and specific provisions of this protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements.

3.1.4 Subject Information and Consent

All subjects must provide written informed consent in accordance with the site's IRB, using an IRB-approved informed consent form. Trial-specific procedures beyond standard of care must not be performed until a signed informed consent has been obtained. The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions for the patient. If the patient agrees to participate, the informed consent form must be signed and personally dated by the patient or legally authorized representative. The person obtaining informed consent must also sign the informed consent form prior to any trial-related procedures. Any additional persons required by the site's IRB to sign the informed consent form must also comply. The consent process should be documented in the patient's medical record.

All subjects are to be fully informed and trial conduct must be in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

Subject confidentiality will be maintained throughout the clinical trial in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject.

Data relating to the trial might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject's privacy is guaranteed. "Protected Health Information" will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

3.2 Trial Administration

3.2.1 Steering Committee

A Steering Committee will provide oversight of the Medtronic CoreValve® U.S. Pivotal Trial as well as issues relating to study enrollment and quality performance at individual sites. The Steering Committee will consist of, at a minimum, the following individuals:

- Medtronic Membership:
  - Committee Chairperson
  - Clinical & Medical Leadership
  - Facilitator
- Non-Medtronic Membership:
  - National Principal Investigators (Interventional Cardiologist and Cardiac Surgeon)
  - Selected Clinical Site Investigators
    - Cardiac Surgeon
    - Interventional Cardiologist

The functions of the Steering Committee include, but are not limited to the following:

- Provide oversight and direction for the trial
- Review of trial enrollment and trial progress
- Support site investigators in resolving any clinical or procedural issues that may impact patient well-being or integrity of the study
- Participate in investigator meetings with case review, protocol insights, etc.
- Review of Data Safety Monitoring Board (DSMB) recommendations
- Assist with publication efforts

The Steering Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. The Steering Committee charter will be approved by Medtronic and the Steering Committee members.

3.2.2 Screening Committee

The Medtronic CoreValve® U.S. Pivotal Trial Screening Committee will ensure appropriate and consistent patient selection across all sites for the Medtronic CoreValve® U.S. Pivotal Trial. The Screening Committee will consist of

Medtronic CoreValve® U.S. Pivotal Trial investigators (interventional cardiologists and cardiac surgeons) and Medtronic CoreValve® proctors. Final decisions on patient eligibility will be made by two cardiac surgeons and one interventional cardiologist on the Screening Committee.

Prior to the onset of the trial, the Screening Committee will establish a charter that outlines their roles and responsibilities and describes the Screening Committee process. The Screening Committee charter will be approved by Medtronic and the Screening Committee members.

3.2.3 Training and Education Committee

The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support and Medtronic CoreValve® proctors for transition of sites from the roll-in phase to the randomization phase of enrollment. The Committee will also review recommendations made by the Data Safety Monitoring Board (DSMB) after their scheduled reviews. It is the responsibility of the Training and Education Committee to make recommendations relative to the augmentation of physician training at a site level, as well as across the trial as a whole. The Training and Education Committee will consist of experienced Medtronic CoreValve® implanters and Medtronic CoreValve® U.S. Pivotal Trial investigators.

Prior to the onset of the trial, the Training and Education Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. The Training and Education Committee charter will be approved by Medtronic and the Training and Education Committee members.

3.2.4 Publication Committee

The Medtronic CoreValve® U.S. Pivotal Trial Publication Committee will review and approve publication ideas and facilitate submissions, including abstracts and manuscripts. The Publication Committee will consist of Medtronic CoreValve® U.S. Pivotal Trial investigators (interventional cardiologists and cardiac surgeons) and Medtronic representatives.

The Publication Committee will establish a plan that outlines their roles and responsibilities and describes the planned frequency of meetings. The Publication Committee plan will be approved by Medtronic and the Publication Committee members.

3.3 Methodology

3.3.1 Purpose

To evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. The total trial duration is expected to be approximately seven years.

3.3.2 Patient Population

Subjects with symptomatic severe aortic stenosis (AS), necessitating aortic valve replacement whose predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.

3.3.3 Design

Subjects will be randomized on a 1:1 basis to either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or to surgical aortic valve replacement (SAVR).

3.3.4 Investigational Sites

The trial will be conducted at up to 45 investigational sites in the United States.

3.3.5 Number of Subjects

Roll-in cases:	3 per implanting site (inclusive of both High Risk Surgical and Extreme Risk patient populations and separate from evaluable sample size)
Proctored cases:	minimum of 5 per site (inclusive of the 3 roll-in cases)
Sample size:	790 (395 MCS TAVI: 395 Surgical Aortic Valve Replacement (SAVR)) and up to 40 additional subjects enrolled with approximately 20 subjects randomized to TAVI and receiving a 23mm valve Non-ilio-femoral will be limited to no more than 30% (249) of the 830 randomized subjects

3.3.6 Inclusion/Exclusion Criteria

To participate in this trial, the subject must meet ALL of the following inclusion criteria:

1. Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.
2. Subject has senile degenerative aortic valve stenosis with:
   - mean gradient > 40 mmHg, or jet velocity greater than 4.0 m/sec by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterization (either resting or dobutamine stress), AND
   - an initial aortic valve area of ≤ 0.8 cm^2 (or aortic valve area index ≤ 0.5 cm^2/m^2) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization
3. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.

4. The subject or the subject's legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site.

5. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.

Subjects are NOT eligible of trial participation if they meet ANY of the following exclusion criteria:

Clinical

1. Evidence of an acute myocardial infarction ≤ 30 days before the intended treatment.
2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure including bare metal stents. Additionally, any drug eluting stents placed within 6 months prior to the index procedure.
3. Blood dyscrasias as defined: leukopenia (WBC < 1000mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy.
4. Untreated clinically significant coronary artery disease requiring revascularization.
5. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
6. Need for emergency surgery for any reason.
7. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram.
8. Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA).
9. End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.
10. Active Gastrointestinal (GI) bleeding within the past 3 months.
11. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
    - aspirin
    - heparin (HIT/HITTS)
    - nitinol (titanium or nickel)
    - ticlopidine and clopidogrel
    - contrast media
12. Ongoing sepsis, including active endocarditis.
13. Subject refuses a blood transfusion.
14. Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.
15. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent.

16. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
17. Currently participating in an investigational drug or another device trial.
18. Symptomatic carotid or vertebral artery disease.
19. Subject has been offered surgical aortic valve replacement but declined.

Anatomical

20. Native aortic annulus size < 18 mm or > 29 mm per the baseline diagnostic imaging.
21. Pre-existing prosthetic heart valve in any position.
22. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)).
23. Moderate to severe (3-4+) mitral regurgitation or (4+) tricuspid regurgitation.
24. Moderate to severe mitral stenosis.
25. Hypertrophic obstructive cardiomyopathy.
26. New or untreated echocardiographic evidence of intracardiac mass, thrombus or vegetation.
27. Severe basal septal hypertrophy with an outflow gradient.
28. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access).
29. Ascending aorta that exceeds the maximum diameter for any given native aortic annulus size (see table below)

Aortic Annulus Diameter	Ascending Aorta Diameter
18 mm – 20 mm	>34 mm
20 mm – 23 mm	>40 mm
23 mm – 27 mm	>>43 mm
27 mm – 29 mm	>43 mm

30. Congenital bicuspid or unicuspid valve verified by echocardiography.
31. Sinus of valsalva anatomy that would prevent adequate coronary perfusion.

Vascular

32. Transarterial access not able to accommodate an 18Fr sheath.

3.3.7 Informed Consent

Prior to enrolling in the trial, patients should be fully informed of the details of trial participation as required by applicable regulations, the site's Institutional Review Board (IRB) and by Medtronic, Inc. Informed consent must be obtained from each patient or legally authorized representative prior to conducting any protocol-

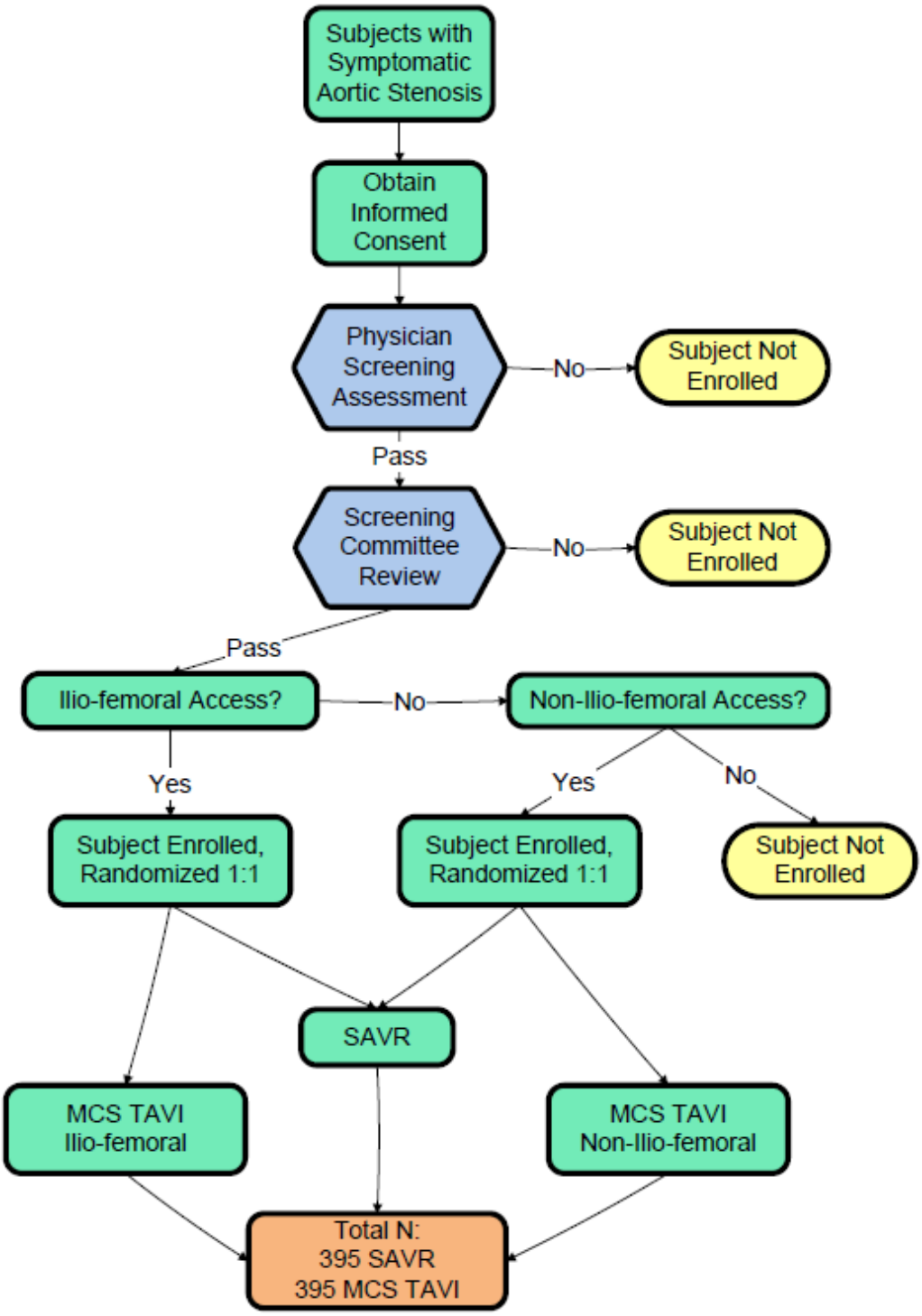
induced activities beyond standard of care, by using the informed consent form (ICF) approved by that site's IRB and by Medtronic, Inc. The consent form must be signed and dated by the patient or legal representative and by the person obtaining the consent. Any additional persons required by the site's IRB to sign the informed consent form must also comply.

Prior to the patient or legal representative signing the ICF, the Investigator or authorized designee will fully explain to the patient or legal representative the nature of the research, trial procedures, anticipated benefits, and potential risks of participation in the trial. The Investigator or delegate will allow adequate time for the patient or legal representative to read and review the consent form and to ask questions.

Signing the ICF serves to document the written and verbal information that the Investigator or authorized delegate provides to the patient or legal representative, the patient or legal representative's understanding of the information, and their agreement to participate. The Investigator or authorized delegate must document in the patient's medical records that the patient was consented and the date on which the consent was obtained. The original signed consent form will be retained in the patient's trial records. A copy of the informed consent will be provided to the patient or legal representative and a copy placed in the patient's medical record.

3.3.8 Enrollment Flowchart for randomization to MCS TAVI vs. SAVR

Figure 1: Enrollment Flowchart



3.3.9

Trial Training

Protocol-specific training and education of all site staff with roles in this trial will take place during the site initiation visit, and throughout the trial as needed. The sponsor will maintain documentation of attendance at each of these training opportunities. Training will include the specifics of trial conduct, product-specific information, and adverse event reporting. A Medtronic representative may be present at each site's MCS TAVI procedures.

Training for the implanting investigators includes but is not limited to the following:

- On-line training, including
  - Pathophysiology and Natural History of Aortic Stenosis
  - General Product Description
  - Medtronic CoreValve® U.S. Pivotal Trial Inclusion/Exclusion Criteria
- Face-to-face didactic training, including
  - Aortic Anatomy and Current Procedures
  - Medtronic CoreValve® Technology Review
  - Procedure Steps
  - Patient selection
  - Implant procedure – Pre-Procedure, Anesthesia and Post-Procedure Patient Care
  - Device Preparation & Loading
  - Complication Management
  - Clinical Data Overview
- Case observations
- Case proctoring
  - A minimum of 5 procedures will be proctored by a Medtronic-trained physician.
- Training for the full team conducted on-site will include the following:
  - Product Use
  - Procedure Steps
  - Device Preparation & Loading
  - Good Clinical Practice

3.4 Trial Procedures

3.4.1 Screening Procedures

Prior to subject participation in this trial, the Investigator must obtain written IRB approval for the trial protocol, informed consent form, and Health Insurance Portability and Accountability Act (HIPAA) Authorization. The approved consent form should clearly reflect the IRB approval date. The Patient Address Form (PAF) and Medical Billing Release Form should also be completed at this time.

All potential subjects for trial entry must be screened for eligibility. Prior to any trial-specific tests or procedures, written informed consent must be obtained from the subject.

Failure to obtain a signed and hand dated informed consent prior to the procedure constitutes a protocol violation, which is reportable to the IRB and the Food and Drug Administration (FDA).

The following tests and procedures must be performed prior to randomization to verify eligibility. The recommended timeframe for these tests and procedures is approximately 30 days prior to submission to the Screening Committee, unless otherwise specified:

- Clinical assessments including: vital signs and all major systems findings, weight, height and body surface area (BSA); BSA will be calculated from height and weight by use of the formula by Dubois and Dubois (BSA = $0.007184 \times \text{weight [kg]}^{0.425} \times \text{height [m]}^{0.725}$)], Grip Strength Test, Gait Test, and Mini Mental Status Exam (MMSE-2E).
- NYHA classification
- STS Risk Score Assessment
- Routine laboratory tests (most recent) including complete blood count (CBC), creatinine, cardiac enzymes CK (and CK-MB if CK is elevated ≥ 2X the laboratory upper limit of normal), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.
- Subject demographics, medical history, risk factors targeted to cardiovascular disease
- 12-lead Electrocardiogram
- Cardiovascular imaging studies:
    - Comprehensive transthoracic 2D echocardiogram (TTE). The TTE must be performed within 45 days prior to submission to the Screening Committee. (Note: if patient recently underwent BAV, a TTE should be obtained post-BAV; within 45 days prior to submission to the Screening Committee). Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
    - Screening Computed Tomography (CT) angiograms (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.

      If the CT angiogram was conducted in the last 365 days and subject has not had a peripheral vascular intervention since the time of the image, a more recent exam is not required as long as visualization of both iliacs and femorals (and subclavian/axillaries, if

applicable) to the aorta can be viewed. However, if the subject had a peripheral vascular intervention within the 365 day window, angiography obtained at the completion of the procedure may be used as an alternative to a repeat CT scan provided it has been obtained within 90 days of submission to the Screening Committee.

- Selective coronary arteriography to assess the presence and severity of coronary artery disease which should include angiograms of both coronary arteries and all bypass grafts (if applicable).

  If the coronary arteriogram has been performed within the last 365 days and the subject qualifies for the study (no significant coronary artery disease), a more recent exam is not required. However, if the subject had evidence of significant coronary artery disease and/or received a coronary intervention within the 365 day window, angiography obtained at the completion of the procedure may be used as an alternative provided it has been obtained within 90 days of submission to the Screening Committee.

- Modified Rankin Scale (for subjects with history of stroke only)
- Logistic EuroScore

Two cardiac surgeons and one interventional cardiologist at each participating site must evaluate each patient for inclusion into the appropriate cohort (High Risk Surgical vs. Extreme Risk) and are required to sign off on the Screening Worksheet to be submitted to the Screening Committee. In addition, each patient must be examined in-person by at least one of the cardiac surgeons to evaluate the risk and determine eligibility for the study. The final eligibility for each subject will be confirmed by the Screening Committee. Additional assessments may be performed to evaluate risk and vascular access, including (but not limited to) pulmonary function test and BNP labwork.

3.4.2 Screening Committee Procedures

The Medtronic CoreValve® U.S. Pivotal Trial Screening Committee will review screening information to make the final determination regarding eligibility of the prospective subject to be enrolled in the Medtronic CoreValve® U.S. Pivotal Trial.

The following information should be submitted to the Screening Committee:

- Completed Patient Screening Worksheet including, but not limited to:
  - Demographics
  - Clinical Assessments including: Vital Signs, Grip Strength Test, Gait Test, and Mini Mental Status Exam (MMSE-2E)
  - Surgical Risk Assessment
  - Case Planning

  Medical History and Co-Morbidities

- Anatomical Measurements

- DICOM-compatible images and cines of all screening exams:
  - Comprehensive transthoracic 2D echocardiogram (TTE). The TTE must be performed within 45 days prior to submission to the Screening Committee. (Note: if patient recently underwent BAV, a TTE should be obtained post-BAV; within 45 days prior to submission to the Screening Committee). Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8.
  - Screening CT angiography (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.
  - Selective coronary arteriography to assess the presence and severity of coronary artery disease which should include angiograms of both coronary arteries and all bypass grafts (if applicable).
- STS calculation print out

3.4.3 Roll-in Cases

The first three successfully enrolled patients at each implanting site inclusive of both High Risk Surgical and Extreme Risk patient populations will be considered "roll-in" subjects, will not be randomized, and will automatically be assigned to MCS TAVI. A maximum of three roll-in subjects is allowed per site. The purpose of the roll-in subjects is to provide the investigators the time for training and familiarization with the protocol and devices. The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support, Medtronic CoreValve Proctors and the Steering Committee for transition of sites from the roll-in phase to the randomization phase of enrollment after the first three subjects have been treated.

A successful roll-in patient, which counts towards the limit of three roll-in patients, is defined as the patient leaving the procedure room with one CoreValve device in the correct position and not requiring emergency surgery. An unsuccessful roll-in patient, which does not count towards the limit of three roll-in patients, is defined as any patient taken to the procedure room for the purpose of CoreValve implantation, but does not leave the procedure room with one CoreValve device in the correct position or requires emergency surgery.

A site must have three successful roll-in patients before they can be evaluated to move into the randomization phase. The Training and Education Committee will review and document their decisions based on the technique of the investigators, as well as the frequency, severity and nature of events in the roll-in subjects.

Subjects enrolled as roll-in subjects will be followed for safety following the same schedule as subjects who are randomized to MCS TAVI. However, the results for the roll-in population will be analyzed separately from the Pivotal trial subjects.

3.4.4 Enrollment and Randomization

Prior to randomization of a subject, the following must occur:

- Confirm patient signed informed consent.
- Confirm patient meets all of the inclusion and none of the exclusion criteria, (with the exception of a percutaneous coronary or peripheral intervention and evidence of an acute myocardial infarction which must not occur within 30 days prior to the index procedure) including approval by the Screening Committee.

Due to the inclusion/exclusion criteria, not all subjects that consent to the trial will be enrolled. All sites will be required to maintain a record of patients screened for the trial meeting general inclusion criteria who have signed the approved informed consent document. For subjects that do not meet trial criteria, the reason for not continuing in the trial must be documented on the screening log in IXRS. Randomization will occur only if the patient meets all inclusion criteria and does not meet any exclusion criteria and has been assessed by the Screening Committee as being an appropriate candidate for enrollment in the Medtronic CoreValve® U.S. Pivotal Trial.

Subjects will be considered enrolled into the trial at the time of randomization. Enrollments shall not exceed 20% (158) of randomized subjects at any individual site. Subjects must have their MCS TAVI or SAVR procedure no later than 30 days post-randomization. Any events or hospitalizations occurring prior to these index procedures will not be counted as part of the primary endpoint. If a subject remains hospitalized beyond 30 days after device placement, this counts as an aortic valve disease hospitalization secondary endpoint occurring on day 31.

Trial randomization will not be blinded. Once randomization is complete and a treatment arm is assigned, crossover from SAVR to TAVI treatment is not permitted. The sponsor will maintain strict device accountability to ensure that only those subjects randomized to the MCS TAVI treatment arm receive the Medtronic CoreValve® PAV.

Distribution of the subjects within the trial groups will be controlled at the implanting sites by means of central randomization using interactive voice/web randomization service (IXRS). The randomization scheme will be securely stored at the IXRS provider (Appendix 17.11).

Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by investigational site and by intended access site (ilio-femoral or non-ilio-femoral) will be used to ensure subjects will be allocated to each comparison group proportionately. Non-ilio-femoral will be limited to no more than 30% (264) of the 880 randomized subjects.

Baseline

Baseline assessments must occur within 14 days after enrollment and include:

- Brief physical examination including vital signs and all major systems findings
- NYHA classification
- 12-lead Electrocardiogram
- Routine laboratory tests including complete blood count (CBC), creatinine, B-type natriuretic peptide (BNP), plasma-free hemoglobin, Cardiac Enzymes CK (and CK-MB if CK is elevated ≥ 2X the laboratory upper limit of normal), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin
- For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.
- NIH Stroke Scale
- A six minute walk test per the American Thoracic Society Guidelines (detailed instructions can be found in Appendix 17.15), will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with O_2 desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form.
- Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
- Assessment of concomitant medications
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admission to the catheterization suite and deaths.
    - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.
- Document any changes to subject condition that affect inclusion/exclusion criteria

3.4.5 Medtronic CoreValve® System TAVI or Surgical Aortic Valve Replacement (SAVR) Procedure

3.4.5.1 MCS TAVI

The following procedures are recommended for MCS TAVI subjects. The Instructions For Use (IFU) and Medtronic CoreValve® Proctors may also be consulted for additional guidance. Refer to Table 2: Schedule of Assessments for data collection requirements. Items indicated below in bold are required for CRF completion.

Pre-Procedure

- If the patient is currently on warfarin therapy prior to the procedure it is recommended to
  - Discontinue warfarin 3 days prior to the procedure
  - Confirm that the INR < 1.8 prior to the procedure
  - aspirin (81- 325 mg) or clopidogrel (75 mg) daily or ticlopidine if clopidogrel is contraindicated) for 3 days prior to the procedure.
- If the patient is currently not on warfarin therapy prior to the procedure
  - aspirin (81-325 mg) on the day of the procedure and clopidogrel, 300 mg
- Consider adjunctive proton pump inhibitors, H_2 antagonists or antacids
- **Routine laboratory tests including complete blood count (CBC), BNP, plasma free hemoglobin, international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.**
- **Cardiac enzymes CK (and CK-MB if CK is elevated ≥ 2X the laboratory upper limit of normal) obtained within 48 hours of the procedure.**
- Perform 12-lead Electrocardiogram
- **Check serum creatinine and creatinine clearance.**
  - If the GFR < 60 cc/min, consider:
    - Fluid hydration on the day prior to the procedure
    - Discontinuation of NSAIDs and ACE inhibitors

MCS TAVI Procedure

Subject must meet all inclusion/exclusion criteria at the time of procedure

- *Joint Participation*
  - The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of transcathether aortic valve replacement (TAVR).
- *Medications*
  One hour prior to the procedure, prophylactic antibiotic therapy of the Investigator's choice should be initiated:
  - Cefuroxime 750mg IV 1 hour pre-procedure, then 6 hours and 12 hours post-procedure
  - If allergic to Penicillin, prescribe Vancomycin 1g IV,

- Consider holding anti-hypertensives

- *Anesthesia and Procedural Set Up*
  - Establish a central venous line.
  - Administer general anesthesia or conscious sedation per hospital protocol
  - Prior to beginning the Medtronic CoreValve® System implant, place a temporary 4-5 Fr. balloon-tip pacing wire in a stable location within the right ventricular (a screw-tip wire may be used for more secure placement for subjects at high-risk for dislodgement, if necessary)
  - Whenever possible, use the upper torso venous system (e.g., jugular, subclavian) for temporary pacing wire access.
  - Use fluoroscopy to guide wire placement and stability
  - Confirm sensing and capture
  - Program the backup pacing rate to minimize ventricular pacing (e.g. 30-40 bpm). If heart block develops, adjust the rate accordingly
  - Record ECG
  - **Record angiogram (Peri-procedural angiographic cine film in DICOM format) during the procedure**

- *Vascular Access*
  - The primary access artery will be used to introduce the CoreValve device and the balloon catheter; the secondary access artery will be used to introduce the reference pigtail.
  - Insert a 6-Fr introducer sheath into the secondary access artery.
  - Insert 18 Fr introducer sheath into the primary access artery using hospital protocol (either percutaneously or surgical cut down)
  - Administer anticoagulant therapy according to hospital protocol. If heparin is administered as an anticoagulant, check activated clotting time (ACT) at five minutes and monitor every 30-60 minutes after initial bolus of heparin
  - Maintain ACT ≥ 250 seconds
  - Anticoagulant may be administered at any time prior to this point, but avoid delaying beyond this point

- *Crossing the native valve*
  - Advance the graduated pigtail catheter to the ascending aorta and position the distal tip in the noncoronary cusp of the native aortic valve
  - Identify the ideal annular viewing plane using contrast injections at various angiographic angles, preferably in the left anterior oblique (LAO) projection
  - Insert an angiographic catheter over a standard, J-tip guidewire into the primary access sheath and advance to the ascending aorta

- Exchange the J-tip guidewire for a 0.035-in (0.889-mm) straight-tip guidewire. Advance the straight-tip guidewire across the native aortic valve into the left ventricle
- After crossing the native aortic valve with the guidewire, advance the angiographic catheter into the left ventricle
- Exchange the straight-tip guidewires for an exchange-length J-tip guidewire
- Exchange the angiographic catheter for a 6 Fr pigtail catheter
- Remove the guidewire and connect the catheter to the transducer. Using both catheters, record the aortic pressure gradient.
- Using a right anterior oblique (RAO) projection, advance previously pigtail-shaped, 0.035-in (0.889-mm) high-support guidewire through the pigtail catheter and position in the apex of the left ventricle.
- Remove the pigtail catheter while maintaining guidewire position in the left ventricle

- *Rapid Pacing and Pre-dilatation of the Implant site*
  - Insert the valvuloplasty balloon through the 18 Fr introducer sheath and advance it to the ascending aorta
  - Perform a rapid pacing test. A successful test is defined as 1-to-1 pacing capture with an immediate drop in pressure and elimination of the systolic-diastolic waveform.
  - Reposition the angiographic equipment to the ideal viewing plane as previously described. Position the valvuloplasty balloon across the native valve, while maintaining strict fluoroscopic surveillance of the distal tip of the guidewire in the left ventricle (LV)
  - Perform BAV per hospital protocol and remove the valvuloplasty balloon while maintaining guidewire position across the native aortic valve
  - Balloon sizing directed to 1:1 sizing of the minimal annular diameter by CTA or echocardiogram with maximum 25 mm balloon
  - Perform full balloon expansion

- *Medtronic CoreValve® Implantation*
  - Insert the device over the 0.035-in (0.889-mm) guidewire and advance it, while maintaining strict fluoroscopic surveillance of the guidewire in the LV
  - When crossing the aortic arch, control the guidewire preventing it from moving forward
  - Advance the device through the native valve. Perform an angiogram to confirm that the graduated pigtail catheter is in position within the noncoronary cusp of the aortic root, preferably in the shallow LAO projection
  - Use Fluoroscopy to identify the appropriate landmarks.
  - Place the bioprosthesis within the aortic annulus (4 mm - 6 mm below the annulus). The annulus is defined as the angiographic floor of the aortic root.

- After attaining optimal catheter position, slowly turn the micro knob and begin to deploy the bioprosthesis. As the inflow aspect of the bioprosthesis starts to flare outward, monitor bioprosthesis position under fluoroscopy
- Caution: During implantation, if resistance to deployment is encountered (for example, the micro knob starts clicking or is tight or stuck), apply mild upward pressure to the macro slider while turning the micro knob. If the bioprosthesis still does not deploy, remove it from the patient and use another system
- Perform an angiogram. Once annular contact is made, the bioprosthesis should not be advanced into a lower position.
- Continue deploying rapidly to the 2/3 deployment point; stop turning the micro knob
- Perform an angiogram to assess the location of the bioprosthesis. Optimal placement of the bioprosthesis is within the aortic annulus (4 mm - 6 mm below the annulus).
- If the bioprosthesis is positioned low, carefully pull the DCS to reposition the bioprosthesis.
- Evaluate the valve position and valve function using hemodynamic, aortography, and possible echocardiography.
- When satisfactory position is achieved, continue to turn the micro knob until both frame loops disengage.
- Use orthogonal views under fluoroscopy to confirm that the frame loops have detached from the catheter tabs. If a frame loop is still attached to a catheter tab, under fluoroscopy, advance the catheter slightly and, if necessary, gently rotate the handle clockwise (<180°) and counterclockwise (<180°) to disengage the loop from the catheter tab.
- Withdraw the DCS carefully to the aorta avoiding contact with the inflow portion of the frame

- *Post Deployment*
  - Withdraw the DCS to the aorta, while maintaining guidewire position.
  - Close the DCS capsule and remove the DCS through the 18 Fr introducer sheath.
  - Advance a 6-Fr pigtail catheter over the guidewire into the left ventricle.
  - Remove the guidewire and connect the pigtail catheter to the transducer.
  - Using both pigtail catheters, record aortic pressure gradient.
  - Withdraw 6-Fr pigtail.
  - Perform postimplant aortogram with the reference pigtail to assure coronary patency and assess aortic regurgitations.
  - Remove the 18-Fr introducer sheath and complete the puncture site closure per hospital protocol.
  - Perform contrast angiography of the primary vessels to verify the absence of any vascular complications with the reference pigtail.

- Remove the reference pigtail catheter over a standard guidewire.
- Remove the 6 Fr introducer and close the access site per hospital protocol.

Ballooning as needed during the implant procedure is standard practice and should not be considered a reintervention.

Immediate Post-Procedure

The procedure is considered complete after final angiography has been performed, and the introducer sheath has been removed from the subject. Thereafter, if an introducer sheath is re-introduced, this is considered a repeat intervention, which must be documented on the reintervention eCRF.

- Anticoagulants should be discontinued per hospital standard.
- Activated clotting time (ACT) should be monitored per hospital standards but recommendation is >250 seconds.
- **Cardiac Enzymes: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated ≥2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.**
- **12-lead Electrocardiogram (performed within 48 hours post MCS TAVI)**
- **NIHSS should be administered within 24 hours post-procedure**
- **Modified Rankin Scale (for patients with a suspected or new neurological event only)**
    - **For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.**
- **An echocardiogram must be done 24-48 hours post-procedure to assess device success.**
- It is recommended that subjects are treated for a minimum of three months with dual anti-platelet medication.
    - if the patient is on warfarin therapy post-procedure:
        - it is recommended that subjects are prescribed either daily aspirin (≥81 mg) or daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.
    - If the patient will not be on warfarin therapy post-procedure:
        - it is recommended that subjects are prescribed daily aspirin (≥ 81 mg) and daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.
- **Assessment of concomitant medications must be performed**

- **For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction within 48 hours post procedure (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.**
- **Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.**
    - **Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.**

Post-Procedure Pacing guidelines

- All patients should stay on telemetry until discharge
- Maintain temporary pacing until at least 48 hours post-implant in CV-ICU unless patient has a pre-existing permanent pacemaker or defibrillator
- After 48 hours, obtain Electrocardiogram (ECG) and assess patient rhythm and conduction
- Based on assessment, and with the consult of an electrophysiologist as needed, take one of the following actions:
    - Discontinue temporary pacing
    - Continue temporary pacing for another 24 hours (longer if needed) to make further assessments
    - Place a permanent pacemaker according to ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (Class I or IIb for Acquired Atrioventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block)
    - **Prior to the permanent pacemaker implantation, document the reason for the placement of the permanent pacemaker via a 12-lead ECG.**
    - For complete heart block, review patient medications.
    - Consider withholding some medications to assess for patient’s intrinsic rate and conduction.
    - If heart block persists off medications, a permanent pacemaker should be considered.
    - If a permanent pacemaker is required, a dual chamber system is recommended to optimize patient hemodynamics.
    - If a permanent pacemaker is implanted, perform a device interrogation and an assessment of AV conduction post insertion and prior to hospital discharge as well as at every follow-up visit to evaluate device utilization (Refer to the Pacing Guidelines in Appendix 17.14).

Assessments done at discharge

Prior to hospital discharge (or no later than 7 days post-MCS TAVI, whichever occurs first) the following tests and procedures must be performed and data collected:

- **Brief physical examination including vital signs and all major systems findings**
- **Routine laboratory tests including CBC, creatinine, BNP, hemoglobin and plasma-free hemoglobin.**
- **12-lead Electrocardiogram**
- **Comprehensive transthoracic 2D echocardiogram (TTE). The TTE should be performed as close to discharge (or no later than 7 days, whichever is sooner) as possible. Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.**
- **NIH Stroke Scale**
  - **Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.**
- **Modified Rankin Scale (for subjects with a suspected or new neurological event only)**
  - **Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.**
- **Concomitant Medications Assessment**
  - **All medications administered during this trial will be recorded in the subject's medical record.**
  - **Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins and anti-platelets) must be reported on the eCRF through at least the 12 month follow-up assessment.**
- **Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.**
  - **Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.**
- **For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.**

3.4.5.2 Surgical Aortic Valve Replacement

Subjects randomized to SAVR should be treated according to the surgeon and hospital's standard practices. Subject must meet inclusion/exclusion criteria at the time of procedure. The SAVR procedure must be an isolated procedure (no concomitant procedures).The surgeon or co-surgeon performing the SAVR must be a trial investigator for the site.

All medications administered during this trial will be recorded in the subject's medical record. Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins, and anti-platelets) must be reported on the eCRF through at least the 12-month follow up assessment.

Immediate Post-Procedure

The procedure is considered complete at the time of skin closure. Immediately post-procedure the following tests and procedures must be performed and data collected:

- Cardiac Enzymes: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated ≥2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.
- 12-lead Electrocardiogram (performed within 48 hours of SAVR)
- NIHSS should be administered within 24 hours post-procedure
- Modified Rankin Scale (for patients with a suspected or new neurological event only)
    - For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab. A TTE should be performed 24-48 hours post-procedure to assess device success.
- Assessment of concomitant medications must be performed.
- For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction within 48 hours post procedure (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.

- Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.

Assessments done at discharge

Prior to hospital discharge (or no later than 7 days post-procedure, whichever occurs first) the following tests and procedures must be performed and data collected:

- Brief physical examination including vital signs and all major systems findings
- Routine laboratory tests including CBC, creatinine, BNP, hemoglobin, and plasma-free hemoglobin
- 12-lead Electrocardiogram
- Comprehensive transthoracic 2D echocardiogram (TTE) The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab. The TTE should be performed as close to discharge (or 7 days, whichever is sooner) as possible.
- NIHSS
    - NIHSS also to be done within 24 hours of any aortic reintervention
        - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.
- Modified Rankin Scale (for subjects with a suspected or new neurological event only)
    - Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke
- Concomitant Medications Assessment
    - All medications administered during this trial will be recorded in the subject's medical record.
- Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins, and anti-platelets) must be reported on the eCRF through at least the 12 month follow-up assessment.
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.
    - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.

- For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.

3.4.6 Follow-up Evaluations

All trial subjects will undergo follow-up evaluations at the following time points post implant (MCS TAVI or SAVR): 30 days (± 7 days), 6 months (180 ± 14 days), 12 months (365 to 410 days), and annually at 2 years (720 days ± 60 days), 3 years (1080 ± 60 days), 4 years (1440 days ± 60 days) and 5 years (1800 ± 60 days). All of these visits will require the subject to return to the clinic.

The following assessments are required at the 30 day, 6 month and 12 month clinic visits.

- Brief physical examination including vital signs and all major systems findings
- NYHA classification
- 12-lead Electrocardiogram
- Rotational x-ray (12-month visit only and for MCS TAVI patients only)
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
- BNP, hemoglobin, and plasma free hemoglobin
- NIH Stroke Scale
  - NIHSS also to be done within 24 hours of any aortic reintervention
- Modified Rankin Scale (for subjects with a suspected or new neurological event only)
  - Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke
- A six minute walk test per the American Thoracic Society Guidelines (detailed instructions can be found in Appendix 17.15), will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with O_2 desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form. *The six minute walk test is not required at the 6-month visit interval.*

- Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
- Assessment of concomitant medications
- Documentation of all adverse events/serious adverse events including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admission to the catheterization suite and deaths.
    - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.
- For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines, Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.

The following assessments are required at the annual clinic visits at 2, 3, 4 and 5 years.

- Brief physical examination including vital signs and all major systems findings
- NYHA classification
- 12-lead Electrocardiogram
- Rotational x-ray (for MCS TAVI only)
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab through the 2 year follow-up visit.
- BNP, hemoglobin, and plasma free hemoglobin
- NIH Stroke Scale
    - NIHSS also to be done within 24 hours of any aortic reintervention
- Modified Rankin Scale (for subjects with a suspected or new neurological event only)
    - Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke
- Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
- Documentation of serious adverse events, major adverse events, cardiovascular events, device-related events, including device-related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths. Data related to pre-existing adverse events should be reconciled and resolved.

    - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.
- For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines, Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.

3.4.7 Data Collection

All scheduled testing and procedures to be conducted during the screening, index procedure and follow-up assessments are summarized in Table 2.

Table 2. Schedule of Assessments

Testing	Screening	Baseline(< 14 days after enrollment)	Implant Procedure/ Valve Surgery	Immediate Post-Procedure	Discharge (or at 7 days post-procedure whichever occurs first)	1 month (30 days) (± 7 Days)	6 month (180 days) (± 14 Days)	Month 12 (365 to 410 days)	Months 24, 36, 48 & 60 (± 60 Days)
Informed Consent and HIPAA Authorization	X								
Inclusion/Exclusion Criteria	X	X[1]	X[2]						
Demographics and Medical History	X[3]								
Clinical Assessment & Physical Exam	X[3]	X			X	X	X	X	X
Grip Strength Test, Gait Test, and Mini Mental Exam	X[3]								
NYHA Class	X[3]	X				X	X	X	X
Logistic EuroScore	X[3]								
STS Risk Score	X[3]								
Routine Laboratory Tests including Complete Blood Count, Creatinine, & Creatinine Clearance	X[3]	X	X[4]		X				
Cardiac Enzymes CK (CK-MB if CK is elevated)[5]	X[3]	X	X[4]	X[5]					
B-type Natriuretic Peptide, Hemoglobin Plasma Free Hemoglobin		X	X[4]		X	X	X	X	X
International Normalized Ratio, Partial Thromboplastin Time, Liver Panel[6], Albumin	X[3]	X	X[4]						
Electrocardiogram	X[3]	X		X[7]	X	X	X	X	X
Pacemaker/defibrillator interrogation and an assessment of AV conduction [8]		X		X	X	X	X	X	X
Rotational X-ray								(X)	(X)
Transthoracic Echocardiogram (TTE)	X[3]			X[9]	X	X	X	X	X
Computed Tomography (CT) Angiogram[10]	X[3]		(X)[11]						
Coronary Arteriogram	X[3]		(X)						
NIH Stroke Scale[12]		X		X[13]	X	X	X	X	X
Modified Rankin Scale[14]	X[15]								
6 Minute Walk Test		X				X		X	
Quality of Life Questionnaires		X				X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	

Testing	Screening	Baseline(< 14 days after enrollment)	Implant Procedure/ Valve Surgery	Immediate Post-Procedure	Discharge (or at 7 days post-procedure whichever occurs first)	1 month (30 days) (± 7 Days)	6 month (180 days) (± 14 Days)	Month 12 (365 to 410 days)	Months 24, 36, 48 & 60 (± 60 Days)
Adverse Events		X	X	X	X	X	X	X	X[16]

(X) MCS TAVI subjects only (SAVR subjects will not have these assessments)

[1] Document any changes to subject condition that affect inclusion/exclusion criteria

[2] Subject must meet all inclusion/exclusion criteria at the time of procedure

[3]Results should be sent to the Screening Committee for confirmation of eligibility.

[4] Laboratory test results must be performed pre-procedure for subjects randomized to the MCS TAVI or SAVR. CK to be obtained within 48 hours of procedure.

[5]CK obtained 8-12 hours post-procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated (≥ 2X the laboratory upper limit of normal). If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.

[6]Liver panel to include: SGPT (ALT), SGOT (AST), Total Bilirubin, Alkaline Phosphatase.

[7] Electrocardiogram within 48 hours of procedure.

[8] For patients with permanent pacemakers or defibrillators only.

[9]TTE should be done 24-48 hours post-procedure to assess device success.

[10]All subjects should have screening thoracic and abdominal CT angiograms with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus.

[11] Peri-procedural angiographic cine film in DICOM format for CoreValve patients only

[12] NIHSS also to be done within 24 hours of any aortic reintervention.

[13] NIHSS to be done within 24 hours of the procedure.

[14] For subjects with a suspected or confirmed neurologic event, Modified Rankin assessments to be performed at 7 days or discharge (whichever occurs first), 30 days, and 3 months post-neurologic event.

[15] Modified Rankin to be performed at screening for patients with a previous history of stroke only.

[16] All confirmed and/or potential SAEs, MAEs, cardiovascular events, endpoint related events, device-related events, including device-related technical observations, UADEs, all strokes (CVAs) and death reports.

This trial contains a health economics review that will be done to compare the in-hospital and 12 month follow-up medical care resource utilization and cost for patients in each of the treatment groups. As part of this trial, patients will be asked to sign a Medical Billing Release Form. This form will be used by the Health Economics and Technology Assessment Group of the Mid America Heart Institute (MAHI) to collect hospital bills from the patient accounting department at any hospital to which patients are admitted, from the time of enrollment in the Medtronic CoreValve® U.S. Pivotal Trial through the study follow-up period. Resource utilization data should be collected by the site along with clinical data using case report forms. This information will be kept strictly confidential and be used solely to assess the medical expenses which occur as a direct result of

participating in the Medtronic CoreValve® U.S. Pivotal Trial (Refer to Appendix 17.13 for additional information).

3.4.8 Unscheduled Follow-up Assessments

If a subject returns to the institution between their scheduled follow-up visits the visit will be treated as an unscheduled visit and the assessments completed at this visit will be done at the discretion of the investigator. eCRFs are provided for unscheduled visits.

3.4.9 Investigational Product Handling and Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator's copy of the device reconciliation records must document any unused devices that have been returned to the Sponsor as well as all product usage including opened but unimplanted devices.

In the event of a device malfunction of the Medtronic CoreValve® System (MCS) prior to implant or in the event that a Medtronic CoreValve® PAV is explanted after implant (due to reintervention or autopsy), the PAV and/or affected MCS components should be returned to Medtronic to the following:

Medtronic, Inc.
Attn: Explant Lab [PCR#]
1851 E. Deere Avenue
Santa Ana, CA 92705-5720

Additional details surrounding the device return process are contained within the Medtronic explant kit and in Appendix 17.12.

3.4.10 Protocol Deviations

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the trial according to the protocol or the Investigator agreement. Deviations will be reported regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the patient in an emergency.

A protocol deviation form is to be completed for each trial protocol deviation, including, but not limited to:

- Failure to obtain informed consent
- Incorrect version of consent provided to patient
- Failure to obtain IRB protocol review and approval before starting the trial
- Enrollment of patient during an IRB approval lapse
- Clinical investigator exceeding enrollment limits specified by sponsor
- Patient did not meet inclusion/exclusion criteria
- Incorrectly performed testing

- Protocol-required testing and/or measurements not done or performed outside of window
- Source data permanently missing
- UADE not reported in the required timeframe

FDA regulations [21 CFR 812.140] require that the Investigator maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol. Relevant information for each deviation will be documented on a deviation form completed by site personnel and reviewed by the Investigator.

Federal regulations [21 CFR 812.150] require Investigators to obtain prior approval from the sponsor before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well being of a patient in an emergency.

Prior approval by the sponsor is expected in those situations in which the Investigator anticipates, contemplates or makes a conscious decision to depart from procedures specified in the protocol. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, but is still considered a deviation (e.g. a trial subject who fails to attend a scheduled follow-up visit, a trial subject too ill to perform a protocol-required test). To obtain approval, the Investigator must call or email and discuss the potential deviation with the Medtronic trial manager or designee prior to initiating any changes.

FDA regulations require the Investigator to notify the sponsor and the reviewing IRB within 5 working days of the following deviations [21 CFR 812.150]:

- a deviation from protocol to protect the life or physical well being of a patient in an emergency
- failure to obtain an informed consent.

Investigators or an authorized designee must notify Medtronic as soon as possible by calling the trial manager or designee and completing the protocol deviation form.

The Investigator is required to adhere to local IRB procedures for reporting deviations.

The DSMB may review protocol deviations to ensure compliance and overall study integrity.

3.4.11 Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the trial through the last follow-up visit at month 60. Subjects who discontinue participation prematurely after randomization will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total trial subjects. If a trial subject is discontinued from the trial early, a Study Exit eCRF must be completed describing the reason for discontinuation. The trial site and Sponsor will make every effort to have all subjects complete the follow up visit schedule. A subject will not be considered lost-to-follow up unless all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must

include three attempts to make contact via telephone and if contact via phone is not successful, a certified letter from the Principal Investigator must be sent to the subject's last known address. Should both telephone and mail efforts to contact the subjects be unsuccessful, the subject's primary physician should be contacted. Subjects will then be deemed lost to follow up. All contact efforts to obtain follow up must be documented in both the subject's medical records and in the trial eCRFs.

3.4.12 Early Termination or Discontinuation of Trial

Possible reasons for early trial termination include:

- Unanticipated Adverse Device Effects (UADE) present an unreasonable risk to patients.
- Recommendation from DSMB.

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification of the IRBs. The Sponsor will also inform the FDA. If the trial enrollment is terminated early, the follow-up visits will continue for all enrolled subjects.

3.5 Adverse Events

3.5.1 Definitions

The definitions presented in this section allow for a clear understanding of adverse event data collection and subsequent analysis.

3.5.1.1 Adverse Event

An adverse event (AE) is any undesirable experience (sign, symptom, illness, or other medical event) occurring to the subject, and that appears or worsens during the clinical trial, whether or not associated with the investigational products or related procedures.

The following events are expected to occur with any surgical implant and therefore should not be reported as AEs, unless they occur outside of the stated timeframe:

Table 3. Unavoidable AEs

Description of the Event	Timeframe (hours) from the Surgical Procedure
Anesthesia-related nausea and/or vomiting	24
Low-grade fever (<100^{o}F or <37.8^{o}C)	48
Back pain related to laying on the procedure table	72
Incisional pain (pain at access site)	72
Sleep problems or insomnia	72

Mild to moderate bruising or ecchymosis	168

3.5.1.2 Serious Adverse Event

A serious adverse event (SAE) is an event that meets any of the following criteria:

- Results in subject death
- Is life threatening* (i.e., the subject was at risk of death at the time of the event)
- Results in inpatient hospitalization
- Results in prolonged existing hospitalization
- Results in persistent or significant disability**/incapacity
- Results in congenital anomaly/birth defect
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

*A life-threatening adverse event is any adverse event that places the subject, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

**The definition of disability is a substantial disruption of a person's ability to conduct normal life functions.

3.5.1.3 Major Adverse Cardiovascular and Cerebrovascular Events

Major adverse cardiovascular and cerebrovascular events (MACCE) is defined as a composite of:

- All-cause death
- Myocardial infarction (MI)
- All stroke, and
- Reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

3.5.1.4 Major Adverse Event

Major adverse event (MAE) includes:

- MACCE
- Acute kidney Injury
- Cardiac tamponade
- Prosthetic valve dysfunction

- Cardiogenic shock
- Valve endocarditis
- Life-threatening, disabling or major bleeding
- Major vascular complication
- Cardiac perforation
- Device migration/Valve embolism

3.5.1.5 Adverse Device Effect (ADE) or Device-Related Adverse Event

An ADE is an adverse event with a reasonable possibility that the device caused or contributed to the event. During this clinical investigation an event should be considered related to the device when it is the result of the Medtronic CoreValve® System (MCS):

- The percutaneous aortic valve (PAV)
- The delivery catheter system (DCS)
- The compression loading system (CLS)
- The implant procedure

An event should be considered not related to the device when it is the result of:

- A pre-existing medical condition
- A new illness, injury or condition
- Medication

3.5.1.6 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect or UADE is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects” [21 CFR 812.3 (s)].

Those known adverse events related to the device, procedure or therapy are listed in Section 3.5.2.3 and in the Risk/Benefit Analysis section of this document (Section 4).

3.5.1.7 Technical Observation

A technical observation is a defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent. Each technical observation (whether or not associated with any untoward medical occurrence in a subject) will be reported on the Adverse Event (AE) eCRF and tabulated as an AE.

3.5.2 Reporting

Investigators are required to keep records on "all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)" [21 CFR 812.140]. Adverse event collection will begin from the point of study enrollment to study closure. All new or worsening (from baseline) adverse events and technical observations will be captured on the AE eCRF through the 12-month follow-up visit. Once a subject has completed their 12-month scheduled follow-up visit, all confirmed and/or potential serious adverse events, major adverse events, cardiovascular events, endpoint related events, device-related adverse events, including device related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths will be required to be reported. It is the responsibility of the Investigator to assess the subject for adverse events and capture the required adverse event information on the AE eCRF.

Medtronic representatives or their designees will conduct monitoring visits to review source documentation and verify the complete and accurate capturing of adverse events.

The Investigator must also notify the responsible IRB regarding new and significant safety information and any event identified by Medtronic that require expedited FDA reporting as serious, unexpected, and related to the investigational device. It is the responsibility of the investigator to ensure site specific IRB safety reporting requirements are met.

Medtronic Clinical will ensure all device-related adverse events and all procedure-related SAEs are processed according to internal policies and procedures. When necessary, Medtronic Field Assurance will respond to sites in writing with the findings related to the product experiences.

The general procedure for investigators reporting any adverse event is as follows:

- If an adverse event occurs, complete all sections of the Adverse Event eCRF.
- Each unique event/diagnosis must be documented separately.
- Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition.
- The Adverse Event eCRF must be reviewed by the Investigator

Reporting guidelines related to specific types of adverse events are outlined below.

3.5.2.1 Serious Adverse Events (SAEs)

Medtronic recommends that the Investigator notify the sponsor within 3 working days of first learning of any SAE using the electronic data capture (eCRF) system. If necessary, the Investigator may be requested to provide copies of source documentation regarding the event (e.g., physician/nurse notes or summaries).

Medtronic will conduct an evaluation of the event and if it is determined by Medtronic to be a UADE, it will be reported as described in the following sections.

3.5.2.2 Unanticipated Adverse Device Effects

Investigators must report any (potential) unanticipated adverse device effects to Medtronic as soon as possible but no later than within 10 working days after the Investigator first learns of the event [21 CFR 812.150] and to their IRB following the IRB's reporting requirements. UADEs should be reported immediately via telephone as well as on an eCRF. The Investigator should consider the device labeling and the Risk/Benefit Analysis section of this document (Section 4) when determining whether an event is unanticipated or not.

If an event is determined by Medtronic to be a UADE, Medtronic will report the event to all investigators to enable reporting to their respective IRBs. Medtronic will provide this notification within 10 working days after Medtronic first receives notice of the effect. [21 CFR 812.150]

If Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate all investigations or parts of investigations presenting the risk in the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46] Follow-up visits for enrolled subjects will continue according the schedule of assessments.

3.5.2.3 All Other Adverse Events

Medtronic recommends that the Investigator notify the sponsor within 10 working days of first learning of any other AE using the electronic data capture (eCRF) system. If necessary, the Investigator may be requested to provide copies of source documentation regarding the event (e.g., physician/nurse notes or summaries).

3.5.2.4 Anticipated Adverse Events

Potential risks associated with MCS TAVI may include, but are not limited to, the following:

- death
- cardiac arrest
- coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- emergent surgery (eg, coronary artery bypass, heart valve replacement, valve explant)
- multi-organ failure
- heart failure
- myocardial infarction
- cardiogenic shock
- respiratory insufficiency or respiratory failure
- cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricle, myocardium, or valvular structures that may require intervention)
- perforation of the myocardium or a vessel

- ascending aorta trauma
- cardiac tamponade
- cardiac failure or low cardiac output
- prosthetic valve dysfunction including, but not limited to, fracture; bending (out-of-round configuration) of the valve frame; under-expansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction;poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement; regurgitation; stenosis
- thrombosis/embolus (including valve thrombosis)
- valve migration/valve embolization
- ancillary device embolization
- emergent percutaneous coronary intervention (PCI)
- emergent balloon valvuloplasty
- major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding)
- allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- infection (including septicemia and endocarditis)
- stroke, TIA, or other neurological deficits
- permanent disability
- renal insufficiency or renal failure (including acute kidney injury)
- mitral valve regurgitation or injury
- tissue erosion
- vascular access related complications (eg, dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
- conduction system disturbances (eg, atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
- cardiac arrhythmias
- encephalopathy
- pulmonary edema
- pericardial effusion
- pleural effusion
- myocardial ischemia
- peripheral ischemia
- bowel ischemia
- heart murmur
- hemolysis
- cerebral infarction-asymptomatic

- non-emergent reoperation
- inflammation
- fever
- hypotension or hypertension
- syncope
- dyspnea
- anemia
- angina
- abnormal lab values (including electrolyte imbalance)

3.5.2.5 Deaths

The Investigator should notify Medtronic within 3 working days of learning of a subject's death, and their IRB following the IRB's reporting requirements, whether or not the death is related to the investigational device. The Investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the Medtronic CoreValve® System. When an autopsy is conducted, a copy of the report should be provided to Medtronic. Medtronic will evaluate the event and if device-related and unexpected, the event will be reported as a UADE.

Any subject death will be reported on the Study Exit eCRF and accompanied by an Adverse Event eCRF identifying the cause of death.

3.5.3 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all deaths and primary endpoint related adverse events. The CEC will consist of interventional cardiologists, cardiologists and cardiovascular surgeons, including a chairperson, who are not participants in the trial.

The purpose of the CEC is to conduct a medical review and classify/adjudicate, at a minimum, all deaths and/or primary endpoints collected in the trial according to definitions and processes outlined in the Medtronic CoreValve® U.S. Pivotal Trial protocol and the CEC charter, which will be developed and approved by Medtronic and the CEC members.

Events will be reviewed and adjudicated by a minimum of three CEC members, who will meet at regular intervals, via teleconference or in person, as deemed necessary. All other events will be reviewed and adjudicated by qualified internal Medtronic safety individual(s) to ensure they should not be adjudicated by the full CEC and that the events are appropriately classified by the investigator.

Prior to the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify/adjudicate a trial primary endpoint related clinical event. CEC decisions will be documented in meeting minutes, which will be maintained in the trial file.

3.5.4 Data Safety Monitoring Board (DSMB)

An independent, unblinded DSMB will be established and will be comprised of at least 3 experts, including a chairperson. The DSMB will have a minimum of one cardiac surgeon, one interventional cardiologist and one statistician, and will be independent of Medtronic and the trial investigators. Investigators participating in the trial may participate in the meetings to offer clarification surrounding events, but will not have voting privileges. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for DSMB review, chairman appointment and guidelines for trial recommendations. The full DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all adverse events and deaths, and will meet more frequently when needed. Primary and safety-related secondary endpoints may also be reviewed at these meetings. Meetings will consist of both open and closed sessions.

The DSMB will also perform a supplemental review of, at a minimum, all serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members will review the report, and when necessary provide recommendations about the conduct of the study and/or request a full DSMB meeting.

A DSMB charter will be developed and approved by Medtronic and the DSMB members. The committee will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews within the DSMB charter.

Following each full DSMB meeting, the board will report to Medtronic in writing and may recommend changes in the conduct of the trial. These DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping the enrollment in the trial or a specific trial arm, or recommendations about trial conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46]. All clinical sites will be notified of this action.

The DSMB may call additional meetings if, at any time, there is concern about any aspect of the trial. All data presented at the meetings will be considered confidential. Additional details about the DSMB can be found in the DSMB charter.

3.6 Statistical Methods and Analysis

The statistical analyses will be performed by Medtronic employed statisticians and independently verified by the staff of the Biostatistics Department at the Harvard Clinical Research Institute and/or Saint Luke’s Mid America Heart Institute. Subjects will be analyzed using an "as treated" approach as the primary analysis. In addition, all randomized subjects will also be analyzed following the

intent-to-treat (ITT) approach as an adjunctive analysis. For the primary analysis, "as treated" will be defined as when the patient is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed. Using this definition, study subjects will be analyzed according to their first attempted procedure (TAVI or SAVR).

The 23mm valve was not available until late in the study; therefore if approximately 20 23mm CoreValve implants have not occurred at the time of approximately 790 randomized subjects, the 23mm subjects will not be included in the primary analysis. Therefore, up to 40 additional subjects will be randomized with about 20 23mm CoreValve implants. When 1 year data are available for the 23mm valve, the primary and secondary endpoint data will be summarized with descriptive statistics. If appropriate, the 23mm valve subjects will be pooled with the original 790 subjects in the primary analysis dataset and the primary and secondary endpoints will be recalculated. The primary endpoint and the 6 secondary endpoints that include hypothesis testing will be analyzed without adjustments for multiple testing. The hierarchical test procedure described in section 3.6.7 Relevant Statistical Analysis Considerations will be followed for the 6 statistical tests defined in the section (secondary endpoints #5, #8 - 2 test, #9 - 2 tests, and powered secondary endpoint).

3.6.1 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for each of the treatment groups for the intent-to-treat, as treated, and per protocol populations. All continuous variables will be summarized as means, medians, standard deviations and interquartile ranges and compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables will be summarized as frequencies and percentages and compared between treatment groups using Pearson's χ^2 test or Fisher's exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.

3.6.2 Missing Data

Every effort will be undertaken to minimize missing data. Since all-cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. However, if outcome data are missing, Kaplan-Meier rates at 12 months and their standard errors will be used in the calculation of the test statistic. To assess the potential impact of these missing data, a sensitivity analysis will be conducted which will include a complete case, a best-case (assume missing MCS TAVI subjects are alive and SAVR subjects have died), a worst-case (assume missing MCS TAVI subjects have died and SAVR subjects are alive), and a tipping point analysis.

3.6.3 Reports

Medtronic is responsible for the reports cited in Table 4. These reports are subject to regulatory retention and inspection requirements. In addition to the

reports listed in Table 4, FDA or the reviewing IRB may request reports pertaining to any aspect of the clinical trial.

3.6.4 Primary Endpoint

The primary endpoint for the trial is all-cause mortality at 12 months.

3.6.5 Primary Hypothesis and Sample Size Determination

3.6.5.1 Primary Hypothesis

Primary Hypothesis: TAVI with the Medtronic CoreValve® System is **non-inferior** to surgical aortic valve replacement (SAVR) in 12 month all-cause mortality:

H_0: $\pi_{MCS\ TAVI} \geq \pi_{SAVR} + 7.5\%$

H_A: $\pi_{MCS\ TAVI} < \pi_{SAVR} + 7.5\%$

In the above expression $\pi_{MCS\ TAVI}$ and π_{SAVR} denote binary rates of all-cause mortality during a fixed follow-up of 12 months. The one-sided Farrington and Manning test[xxv] for non-inferiority of two binomial proportions will be carried out to assess statistical significance.

Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is **superior** to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer:

H_0: $\pi_{MCS\ TAVI} = \pi_{SAVR}$

H_A: $\pi_{MCS\ TAVI} < \pi_{SAVR}$

This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity.

3.6.5.2 Sample Size Determination

Primary Hypothesis

Assumptions:

1:1 treatment allocation ratio

One-sided alpha = 0.05

$\pi_{SAVR} = 20.0\%$

$\pi_{MCS\ TAVI} = 20.0\%$

Power = >80%

Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, Power Analysis

and Sample Size (PASS) software calculates that a total of **355** subjects in each arm is required to attain 80% power in a test of non-inferiority of the study device at the 0.05 level of significance. Accounting for a 10% drop-out rate or loss to follow-up in each treatment arm, a total of **395**+**395** = **790** subjects is required to have a minimum of 355 subjects in each arm.

Powered Secondary Hypothesis

Assumptions:

1:1 treatment allocation ratio

One-sided alpha = 0.025

π_{SAVR} = 20.0%

$\pi_{MCS\ TAVI}$ = 12.1%

For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), PASS software calculates that 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.

3.6.6 Secondary Endpoints

The secondary endpoints are as follows:

The following secondary endpoints will be compared between MCS TAVI and SAVR subject cohorts:

1. MACCE-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

   MACCE-free survival estimates will be provided for the randomized groups at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.

   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.
2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

   MACCE components will be summarized and MACCE component event-free rates will be provided at 30 days, 6 months, 12 months and annually through 5 years. All subjects will be included in the analysis.

   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.
3. MAE at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

MAE events will be summarized and MAE event-free rates will be provided at 30 days, 6 months, 12 months, and annually through five years. All subjects will be included in the analysis.

The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

4. Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months,12 months and annually thereafter up to 5 years.

   The incidence of conduction disturbance requiring permanent pacemaker implantation will be provided at 30 days, 6 months, 12 months and annually through five years, separately for new onset and pre-existing conduction disturbance. All subjects will be included in the analysis.

   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

   For each subject with paired data, the number of classes changed from baseline (-2, -1, 0, 1, 2, or 3) will be calculated at 30 days, 6 months, 12 months and annually through five years.

   The endpoint will be evaluated using a two-sample t-test or Wilcoxon rank-sum test as appropriate.

6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months

   All subjects who are able to perform the six-minute walk evaluation; and those subjects who are unable to perform the walk evaluation due to heart failure symptoms at the time of the follow-up visit will be included in the analysis.

   The six-minute walk evaluation will be evaluated at 30 days and at 12 months using a two-sample t-test or Wilcoxon rank-sum test as appropriate.

7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.

   The proportion of post randomization days alive out of hospital against total days alive will be compared at twelve months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of days alive as of the follow-up visit date. All hospitalizations will be included in this analysis, including hospitalization for device implant. All subjects will be included in the analysis.

   The endpoint will be evaluated using continuous data analyses such as a two-sample t-test or Wilcoxon rank-sum test.

8. Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

   The Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL will be assessed at baseline, 30 days, 6 months, 12 months and

annually through five years. All subjects completing the questionnaires will be evaluated and the reasons for missing data will be provided.

The changes in QoL scores will be evaluated using a two-sample t-test or Wilcoxon rank-sum test as appropriate.

9. Echocardiographic assessment of prosthetic valve performance at discharge, 30 days, 6 months, 12 months, and annually thereafter up to 5 years using the following measures:
    - transvalvular mean gradient
    - effective orifice area
    - degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular)

    The four echocardiographic measurements will be evaluated at discharge, 30 days, 6 months, 12 months and annually through five years. All subjects undergoing echocardiography procedures will be evaluated.

    All measures will be evaluated using a two-sample t-test or the Wilcoxon rank-sum test for continuous variables, and the Mantel-Haenszel test for categorical variables, as appropriate.
10. Aortic valve disease related hospitalizations

    The number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.

    Hospitalization-free rates will be provided at 30-days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.
11. Cardiovascular deaths and valve-related deaths

    The number of cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months, and annually through five years will be reported. All subjects will be included in the analysis.

    The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.
12. Strokes

    The number of strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually through five years will be reported. All subjects will be included in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.
13. Index procedure related MAEs

    Index procedure-related MAE events will be summarized and event rates will be provided at 30 days. The numerator will be the number of procedure-related MAE events experienced by the end of the follow-up visit, and the denominator will be the number of subjects evaluated at the follow-up visit plus the number of subjects not evaluated but who experienced a procedure-related MAE event prior to the end of the follow-up visit window.

The endpoint is descriptive and no statistical hypothesis test will be performed.

14. Length of index procedure hospital stay

    The length of TAVI or SAVR hospital stay will be summarized for all subjects.

    Descriptive statistics will be provided. The endpoint is descriptive and no statistical hypothesis test will be performed.

    The following secondary endpoints will be assessed for the MCS TAVI cohort subjects only:

15. Device success defined as follows:

    - successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,
    - correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),
    - Intended performance of the prosthetic valve[1] (aortic valve area > 1.2 cm^2 for 26, 29 and 31mm valves, ≥ 0.9 cm^2 for 23mm valve(by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR)
    - Only one valve implanted in the proper anatomical location

[1] assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge

    Device success, as defined above, will be calculated for all subjects undergoing the TAVI procedure.

    The endpoint is descriptive and no statistical hypothesis test will be performed.

16. Procedural success, defined as device success and absence of in-hospital MACCE.

    Procedure success, as defined above, will be calculated for all subjects undergoing the TAVI procedure.

    The endpoint is descriptive and no statistical hypothesis test will be performed.

17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

The number of subjects with evidence of prosthetic valve dysfunction will be evaluated at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.

A Kaplan-Meier survival analysis will be performed. The endpoint is descriptive and no statistical hypothesis test will be performed.

3.6.7 Relevant Statistical Analysis Considerations

All statistical tests and/or confidence intervals, as appropriate, will be performed at α=0.05 (2-sided), except when specified otherwise. All

reported p-values greater than or equal to 0.001 will be rounded to three decimal places. P-values less than 0.001 will be displayed as "<0.001."

Provided the 12-month mortality primary objective is met with a significant p-value, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis and five of the secondary objective hypothesis tests. The goal of this hierarchical procedure is to make statistically valid claims of significance in the device labeling.

In this hierarchical test procedure, each objective is examined in the pre-specified order. The hierarchical testing order will be:

1. Change in transvalvular mean gradient from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level of 0.05 the hypotheses:

$$H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} - 15$$

$$H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} - 15$$

In the above expression $\mu_{MCS\ TAVI}$ and μ_{SAVR} denote the mean improvements in mean gradient from baseline to 12 months measured in mmHg.

2. Change in effective orifice area baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

$$H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} - 0.375$$

$$H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} - 0.375$$

In the above expression $\mu_{MCS\ TAVI}$ and μ_{SAVR} denote the mean improvements in effective orifice area from baseline to 12 months measured in cm^2.

3. Change in NYHA classification from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #5. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

$$H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} - 0.375$$

$$H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} - 0.375$$

In the above expression $\mu_{MCS\ TAVI}$ and μ_{SAVR} denote the mean number of classification improvements in NYHA from baseline to 12 months.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #8. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

$$H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} - 5$$

$$H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} - 5$$

In the above expression $\mu_{MCS\ TAVI}$ and μ_{SAVR} denote the mean improvements in the KCCQ score from baseline to 12 months.

5. Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer. This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity to test the hypotheses:

$$H_0: \pi_{MCS\ TAVI} = \pi_{SAVR}$$

$$H_A: \pi_{MCS\ TAVI} < \pi_{SAVR}$$

In the above expression $\pi_{MCS\ TAVI}$ and π_{SAVR} denote the binary rate of MACCE at 30 days or hospital discharge.

6. Change in SF-12 Physical Summary Scale from baseline to 30 days: TAVI vs. SAVR from secondary objective #8. The two-sided two-sample t-test will be used to test at a level 0.05 the hypotheses:

$$H_0: \mu_{MCS\ TAVI} = \mu_{SAVR}$$

$$H_A: \mu_{MCS\ TAVI} \neq \mu_{SAVR}$$

In the above expression $\mu_{MCS\ TAVI}$ and μ_{SAVR} denote the mean improvements in the SF-12 Physical Summary Scale from baseline to 30 days.

As the trial confirmation is not dependent on the secondary endpoints, multiplicity adjustments will not be made in the analyses of the secondary endpoints. Summary data from other secondary objectives, such as device success and procedural success from secondary objectives #15 and #16, respectively, may be provided in the device labeling. However, no claims of statistical significance or other statistical inference will be made.

A poolability analysis among investigational centers, access site (ilio-femoral or non-ilio-femoral), and primary baseline demographics will be performed for the primary endpoint and will be described in the Statistical Analysis Plan. In particular, the primary endpoint and key secondary endpoints such as MACCE- and MAE-free survival will be examined for differences in outcome between genders and between access sites. Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and gender and between treatment and access site.

3.7 Data and Quality Management

3.7.1 Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection.

3.7.2 Data Collection

Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegation of Authority Log. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the trial.

The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each eCRF.

The sponsor and/or assigned designee will be responsible for the processing and quality control of the data. All trial-related documents must be retained for a period of at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. Medtronic will inform the investigator/institution when these documents are no longer required to be retained.

No trial document or image should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the trial records to another party or move them to another location, advance written notice should be given to the Sponsor.

3.7.3 Core Laboratories Procedures

Data from the core lab will be entered by the core lab and stored in the Oracle Clinical Remote Data Capture system as described in the Medtronic CoreValve® U.S. Pivotal Trial Data Management Plan.

3.7.4 Source Documents

Source documentation is defined as the first time the data appear and may include all clinical records, hospital records, surgery reports, autopsy reports, and any other material that contains original information used for trial data collection or adverse event reporting. No eCRFs may serve as source documents.

Source documentation may vary from site to site.

The source documents must be retained by the investigational site for a period of 2 years after trial conclusion and made available for monitoring or auditing by the sponsor's representative or representatives of the FDA and other applicable regulatory agencies. The Investigator must ensure the availability of source documents from which the information on the eCRFs was derived.

3.8 Records and Reports

3.8.1 Responsibilities of the Sponsor

The Sponsor must maintain the following records:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement
- Curriculum vitae for each Investigator

- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event information
- Complaint documentation
- All data forms, prepared and signed by the Investigators and received source documentation and core lab reports
- Protocol and report of prior investigations
- Site monitoring reports
- Financial disclosure information

The Sponsor is responsible for the preparation of, the accuracy of the data contained in, the review of and the submission of the reports listed in Table 4.

Table 4. Sponsor Reporting Responsibilities

Report	Submit to	Description
Unanticipated Adverse Device Effects (UADE)	IRB, Investigators, FDA	Medtronic will report on any confirmed unanticipated adverse device effect evaluation within 10 working days after first receiving notice of the effect. (21 CFR 812.150)
Withdrawal of IRB approval	IRB, Investigators, FDA	Notification, when appropriate, will be made within 5 working days after Medtronic receives notice of withdrawal of IRB approval.
Withdrawal of FDA approval	IRB, Investigators	Notification will be made within 5 working days after Medtronic receives notice of withdrawal of FDA approval.
Current Investigator List	FDA	Medtronic will submit a current list of the names and addresses of all participating Investigators at six-month intervals, beginning six months after FDA approval of IDE.
Progress Report	IRB, Investigators, FDA	A progress report will be submitted at least yearly.
Recall and Device Disposition	IRB, Investigators, FDA	Notification will be made within 30 working days of Medtronic's request that an Investigator return, repair or otherwise dispose of any devices. Such notification will state why the request was made.
Final Report	IRB, Investigators, FDA	Notification will be made within 30 working days of the completion or termination of the investigation. A final report will be submitted within three months after trial completion or termination.

Report	Submit to	Description
Failure to obtain Informed Consent	FDA	Notification will be made within 5 working days after Medtronic's receipt of such notification indicating Informed Consent was not obtained.
Emergency Deviations from Investigational Plan	FDA	Notification will be made within 5 working days after Medtronic learns of an emergency deviation from the Investigational Plan where the deviation was made to protect the life or physical well being of a subject.

3.8.2 Responsibilities of the Investigator

The Investigator is responsible for the preparation, review, signature, and retention of the records listed below:

- All essential correspondence that pertains to the investigation
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation), including, for example:
    - Signed and dated consent forms
    - Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurses' notes
    - All adverse event information
    - A record of the exposure of each subject to the investigational device (e.g., date of implant procedure and follow-up assessment dates)
    - Documentation of any deviation from the protocol, including the date and the rationale for such deviation
- Signed Investigator Agreement and curriculum vitae
- The protocol and any amendments

The Investigator may withdraw from responsibility to maintain records by transferring custody to another person, who will accept responsibility for record and report maintenance.

The Investigator is responsible for the preparation, review, signature, and submission of the reports listed below in Table 5. These are also subject to inspection by government agencies and must be retained as specified above.

Table 5. Investigator Reporting Responsibilities

Report	Submitted to	Description
Unanticipated Adverse Device Effects (UADE)	Sponsor, IRB	UADEs should be reported immediately via telephone as well as on an eCRF. UADEs must be submitted as soon as possible, but in no event later than10 working days after the Investigator first learns of the effect. (21 CFR 812.150)
Serious Adverse Events and Deaths	Sponsor	Medtronic requests that the Investigator's report on all serious adverse events and deaths be submitted within 3 working days after the Investigator first learns of the event.
Withdrawal of IRB approval	Sponsor	The Investigator must report a withdrawal of the reviewing IRB, approval within 5 working days.
Progress Report	Sponsor, IRB	The Investigator must submit a progress report on an annual basis if the trial lasts longer than one year.

Report	Submitted to	Description
Failure to obtain Informed Consent	Sponsor, IRB	The Investigator must make notification within 5 working days after device implant.
Final Report	Sponsor, IRB	This report must be submitted within 3 months after termination or completion of the investigation.
Deviations from Investigational Plan (CFR 812.150)		
Emergency Use	Sponsor, IRB	Notification must be made within 5 working days of the occurrence of an emergency deviation made to protect the life or physical well-being of a subject.
Planned deviation	Sponsor, IRB, FDA	If the deviation affects scientific soundness of the trial or the rights, safety, or welfare of the subject and is not an emergency, prior approval must be obtained from Medtronic, the reviewing IRB, and FDA.
Other Deviations	Sponsor	Deviations that are beyond the control of the investigator (such as patient who fails to return to follow-up visit) or deviations that do not affect the scientific soundness of the trial or the rights, safety, or welfare of the subject and are not an emergency, should be submitted as they are identified by the site or Medtronic staff

4. RISK / BENEFIT ANALYSIS

4.1 Potential Risks and Discomforts

There are risks for participants in this trial. However, it should be noted that most of the risks of trial participation are not materially different than those entailed by an individual who undergoes the same treatment outside of the context of this trial.

Known adverse events that may result from TAVI include but may not be limited to:

- death
- cardiac arrest
- coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- emergent surgery (eg, coronary artery bypass, heart valve replacement, valve explant)
- multi-organ failure
- heart failure
- myocardial infarction
- cardiogenic shock

- respiratory insufficiency or respiratory failure
- cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricle, myocardium, or valvular structures that may require intervention)
- perforation of the myocardium or a vessel
- ascending aorta trauma
- cardiac tamponade
- cardiac failure or low cardiac output
- prosthetic valve dysfunction including, but not limited to, fracture; bending (out-of-round configuration) of the valve frame; under-expansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction;poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement; regurgitation; stenosis
- thrombosis/embolus (including valve thrombosis)
- valve migration/valve embolization
- ancillary device embolization
- emergent percutaneous coronary intervention (PCI)
- emergent balloon valvuloplasty
- major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding)
- allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- infection (including septicemia and endocarditis)
- stroke, TIA, or other neurological deficits
- permanent disability
- renal insufficiency or renal failure (including acute kidney injury)
- mitral valve regurgitation or injury
- tissue erosion
- vascular access related complications (eg, dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
- conduction system disturbances (eg, atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
- cardiac arrhythmias
- encephalopathy
- pulmonary edema
- pericardial effusion
- pleural effusion
- myocardial ischemia

- peripheral ischemia
- bowel ischemia
- heart murmur
- hemolysis
- cerebral infarction-asymptomatic
- non-emergent reoperation
- inflammation
- fever
- hypotension or hypertension
- syncope
- dyspnea
- anemia
- angina
- abnormal lab values (including electrolyte imbalance)

There have been no voluntary or involuntary regulatory recalls of the Medtronic CoreValve® System in the United States to date. The original 18Fr Delivery Catheter System has been improved with the addition of the AccuTrak™ stability layer which has been added to aid in accuracy in the deployment of the Medtronic CoreValve® PAV. The 31mm and 23 mm valve sizes were added to increase the treatable annulus range. A new Delivery Catheter System (DCS-C4-18FR-23MM) will be used to deploy 23mm Percutaneous Aortic Valve (PAV).There are no other design changes anticipated for the Medtronic CoreValve® System during the clinical trial.

4.2 Methods to Minimize Risks

The investigational plan is specifically designed to manage and minimize risks through careful subject selection, thorough training of investigators, adherence to the pre-determined time points to assess subject clinical status and regular clinical monitoring visits by Sponsor appointed monitoring personnel.

In addition, an independent Data Safety Monitoring Board will monitor safety of the subjects throughout the trial.

4.3 Potential Benefits

The targeted trial population (generally elderly patients of both genders) has been shown to have high mortality if the severe aortic stenosis is left untreated. This population also has high risk for mortality and morbidity if treated surgically or are managed medically. The less invasive investigational treatment of transcatheter aortic valve implantation has shown in research to reduce mortality and morbidity.

5. DESCRIPTION OF MEDTRONIC COREVALVE® SYSTEM

5.1 Investigational Product Description

The Medtronic CoreValve® System (MCS) consists of 3 components: the Percutaneous Aortic Valve Bioprosthesis (PAV) in Figure 2 below, the Delivery Catheter System (DCS) in Figure 3, and the Compression Loading System (CLS) in Figure 4.

Percutaneous Aortic Valve Bioprosthesis

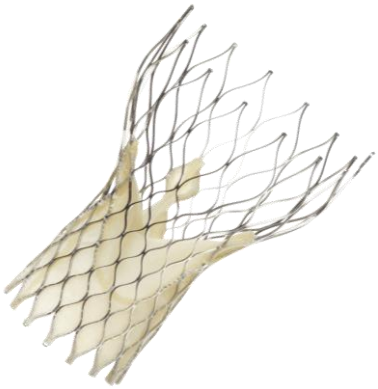


Figure 2: Percutaneous Aortic Valve (PAV)

The PAV is manufactured by suturing valve leaflets and a skirt, made from a single layer of porcine pericardium, into a tri-leaflet configuration. The PAV is designed to replace the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve.

The self-expanding multi-level frame is made of Nitinol and is radiopaque.

The PAV is available to sites with or without an antimineralization treatment of alpha-amino oleic acid (AOA), a compound derived from oleic acid, a naturally occurring long-chain fatty acid.The PAV is available for a range of aortic annulus and ascending aortic diameters as shown in Table 6 below.

Table 6. Patient Anatomical Diameters

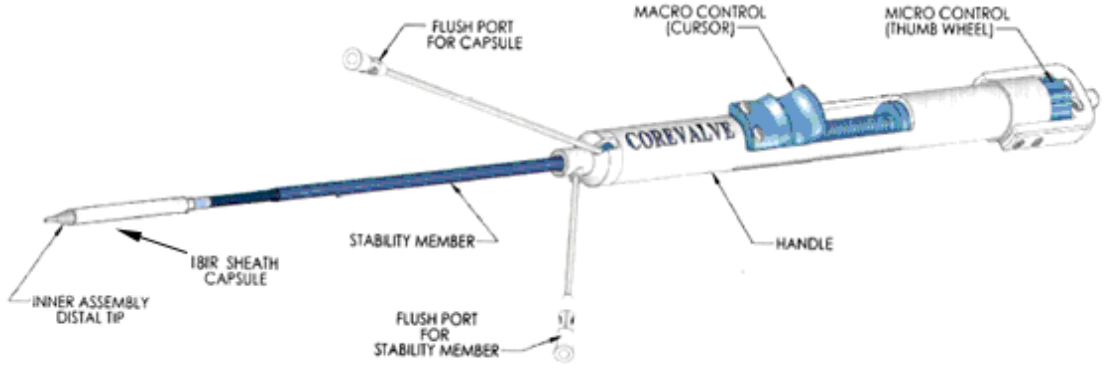
Model	Size (mm)	Aortic Annulus Diameter (range in mm)	Ascending Aortic Diameter (mm)
MCS-P3-2334/ MCS-P4-23-AOA	23	18–20	≤34
MCS-P3-640/ MCS-P3-26-AOA	26	20-23	≤40

MCS-P3-943/ MCS-P3-29-AOA	29	23-27	≤43
MCS-P3-3143/ MCS-P3-31-AOA	31	26-29	≤43

Delivery Catheter System

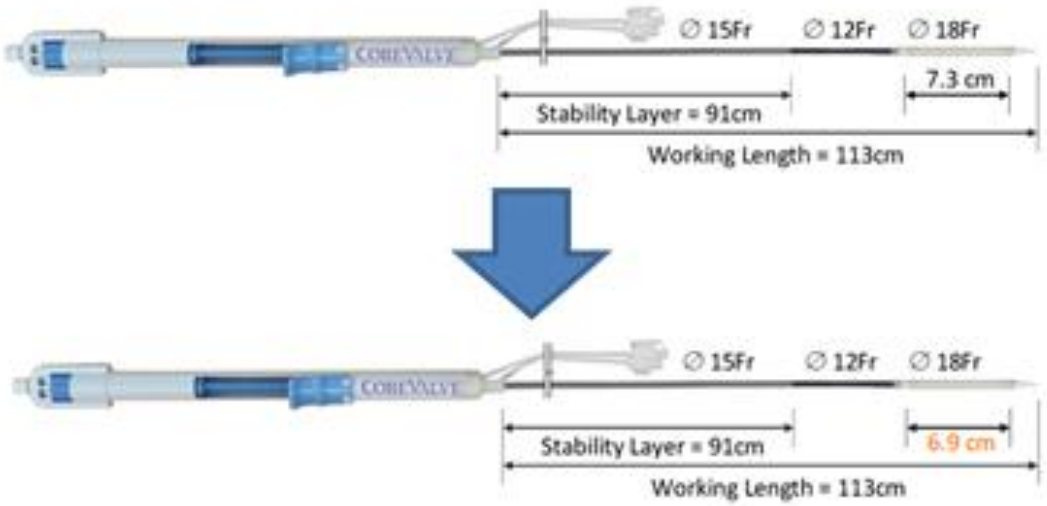
The AccuTrak™ DCS (DCS-C4-18FR) is compatible with a 0.889-mm (0.035-in) guidewire. The working length of the AccuTrak™ DCS is 112.5 cm. It incorporates a protective deployment sheath that houses and deploys the PAV. The AccuTrak™ DCS-C4-18FR can be used to house and deliver the 26mm, 29mm, and 31mm sizes of the PAV. The outer diameter of the DCS is 12Fr, the stability layer is 15Fr and the outer diameter of the valve capsule is 18 Fr.

Figure 3: Delivery Catheter System (DCS)



A new Delivery Catheter System (DCS-C4-18FR-23MM) will be used to deploy 23mm Percutaneous Aortic Valve (PAV). The DCS-C4-18FR-23MM has a shortened Capsule and Plunger (5mm) for delivery of the 23mm PAV but the working length of the new AccuTrak™ DCS is 112.5 cm similar to DCS-C4-18Fr used to deploy other PAV sizes.

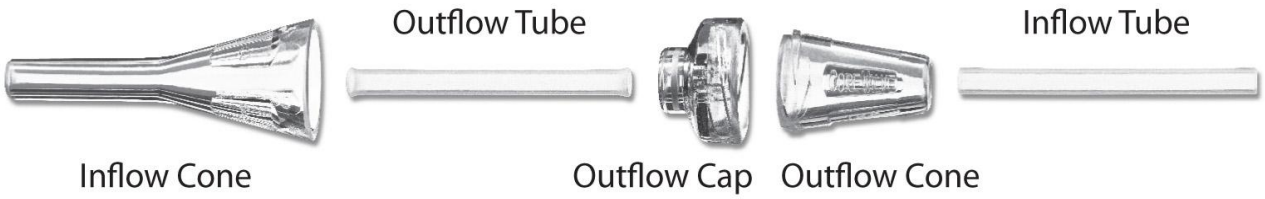
Design Changes for Delivery Catheter System (DCS) specific to 23mm



The AccuTrak™ DCS features an integrated handle designed to provide the user with accurate and controlled deployment. After the DCS is placed in the vicinity of the aortic annulus, the user retracts the deployment sheath, thereby deploying the PAV to the desired location. In use, the deployment sheath can be partially pulled back to evaluate the PAV location prior to fully releasing the PAV. In this way, the user can make slight adjustments to the PAV location if needed prior to release.

Compression Loading System (Model CLS-3000-18 FR)

Figure 4: Compression Loading System (CLS)



The CLS (Model CLS-3000-18FR) compresses the PAV into the DCS. The CLS is comprised of the following elements:

- inflow cone
- inflow tube (straight tube)
- outflow cap
- outflow cone
- outflow tube (tube with flared ends)

Medtronic may incorporate additional devices into this clinical study providing they receive regulatory approval and the scientific soundness of the study is not adversely affected.

5.2 Medtronic CoreValve® Ordering, Storage, and Disposition

Devices will be ordered through Medtronic.

As stated in the Instructions for Use (IFU), the PAV should be stored at 15°C to 25°C (59°F to 77°F). Avoid exposing the PAV to extreme fluctuations of temperature. Avoid freezing the PAV. Appropriate inventory control should be maintained so that PAVs with earlier Use By dates are implanted preferentially. Store the delivery system and compression loading system in a cool, dry environment.

All implanting sites will maintain device logs to document the disposition of all components of the Medtronic CoreValve® System.

6. MONITORING AND AUDITING

6.1 Monitoring

The investigational site will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. A monitoring visit will be conducted primarily to ensure the safety and wellbeing of the subjects is preserved. Monitoring visits will also be used to verify that trial data submitted on case report forms are complete and accurate with respect to the subject records and to verify device accountability. Site personnel will complete eCRFs following each subject visit. Trial data submitted will be reviewed against patient charts and other sources containing original records of patient data. Source document verification will occur in accordance to the CoreValve Monitoring Plan.

The responsible individual for this trial is included on the title page of the CIP.

The progress of the trial will be monitored by:

- On-site review, as deemed appropriate by the sponsor
- Telephone communications between the site personnel (e.g., Investigator, Trial Coordinator) and trial monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

Monitoring and monitoring oversight will be provided by Medtronic CardioVascular (8200 Coral Sea St NE, Mounds View, MN 55112). Representatives of Medtronic (i.e. contractors and designees) may also act as the trial monitors to the site.

6.2 Auditing

Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to verify the performance of the monitoring process and the trial conduct, independently of the personnel directly involved in the trial. Regulatory bodies, such as the Food and Drug Administration, may also perform inspections at participating sites. The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents.

7. LABELING

Instructions for Use and additional labeling are attached in Appendix 17.1.

8. CONSENT MATERIALS

The template consents for the trial are attached in Appendix 17.2.

9. IRB INFORMATION

IRB information is attached in Appendix 17.3.

10. OTHER INSTITUTIONS

Information regarding other institutions involved in this trial is located in Appendices 17.4, 17.8, 17.9, 17.10, 17.11, 17.12, and 17.13.

11. ADDITIONAL RECORDS AND REPORTS

Information regarding additional Records and Reports can be found in Appendix 17.5.

12. REPORT OF PRIOR INVESTIGATIONS

The Report of Prior Investigations is attached in Appendix 17.18.

13. PUBLICATION POLICY

Medtronic, as the Sponsor of this trial, recognizing the seminal importance of this investigation, is committed to the widespread dissemination of all primary and secondary endpoint results. A publication plan will be implemented and followed. At the conclusion of the trial, a multisite abstract reporting the primary results will be prepared by the National Principal Investigators (in collaboration with others including but not limited to the Steering Committee, directors of the core laboratories, CEC, and Lead Investigators from high enrolling sites) and presented at an annual scientific meeting (e.g., Transcatheter Cardiovascular Therapeutics, EuroPCR, the American Heart Association, or the American College of Cardiology). A multisite publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the trial is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

Following analysis and presentation of the primary endpoint results, active participation of all committee members, Investigators from high enrolling sites, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the trial requires approval by the Principal Investigators after review by the Steering Committee.

A separate publication plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data.

14. AMENDMENTS TO THE CLINICAL INVESTIGATIONAL PLAN

All amendments to the CIP shall be agreed between the sponsor and the clinical investigator(s). Amendments will be recorded with a justification for the amendments in the log below:

Version	Description of change
1.0 August 26, 2010	Original version submitted to FDA
2.0 November 2, 2010	Address FDA conditional Approval Letter (October 13, 2010), administrative edits as required
3.0 December 13, 2010	Allow for non-ilio-femoral access, administrative edits as required (this version was not implemented or distributed to sites)
4.0 February 1, 2011	Address FDA conditional Approval Letter (January 14, 2011), administrative edits as required
5.0 May 26, 2011	Allow for additional sites, statistical analysis clarification and administrative edits as required (this version was not implemented or distributed to sites)
6.0 July 11, 2011	Address FDA questions received via email (June 22, 2011). Administrative edits as required
7.0 October 1, 2011	Increase proportion of non-ilio-femoral sample size
8.0 October 10, 2011	Allow for additional valve size, clarifications and administrative edits
9.0 December 5, 2011	Allow for additional valve size, clarifications and administrative edits (this version was not implemented or distributed to sites)
10.0 January 25, 2012	Address FDA questions received via email (January 3, 2012). Administrative edits as required
11.0 July 30, 2012	Increase sample size, CMS reimbursement language and administrative edits.
12.0	Change sample size back to original sample size of 790 subjects.

August 22, 2012	
13.0 January 15, 2013	Incorporated EnVeo™ / G5 delivery system
14.0 February 10, 2014	Update adverse events/risks to align with commercial IFU, add AOA treated valves, remove EnVeo™ / G5 delivery system, update event adjudication requirements, discontinue all Corelab analysis (except Quality of Life) for 3 year, 4 year, and 5 year follow-up visits, clarifications and administrative edits.

15. ABBREVIATIONS AND DEFINITIONS

15.1 List of Abbreviations

Abbreviation	Term
2D	Two dimensional
3D	Three dimensional
AE	Adverse event
ACT	Active Clotting Time
ADE	Adverse Device Effect
AOA	Alpha-amino Oleic Acid
AR	Aortic regurgitation
AS	Aortic stenosis
AVR	Aortic valve replacement
BAV	Balloon Aortic Valvuloplasty
BSA	Body Surface Area
BNP	B-type Natriuretic Peptide
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CLS	Compression loading system
CT	Computed tomography
CVA	Cerebrovascular accident
DCS	Delivery catheter system
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case report form
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FDA	U.S. Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HIT/HITTS	Heparin-Induced Thrombocytopenia / Heparin-Induced Thrombocytopenia and Thrombosis
ICF	Informed Consent Form

IRB	Institutional Review Board
IFU	Instructions for use
ITT	Intent-to-treat
IXRS	Interactive Voice/Web Response System
LBBB	Left Bundle Branch Block
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MACCE	Major adverse cardiovascular and cerebrovascular event
MAE	Major Adverse Event
MCS	Medtronic CoreValve® System
MI	Myocardial infarction
NYHA	New York Heart Association
PAV	Percutaneous aortic valve
PCI	Percutaneous Coronary Intervention
QoL	Quality of Life
RBBB	Right Bundle Branch Block
SAE	Serious adverse event
SAVR	Surgical Aortic Valve Replacement
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implant
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic echocardiography
UADE	Unanticipated adverse device effect

15.2 Definition of Terms

ACUTE KIDNEY INJURY

Acute Kidney Injury will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

Acute Kidney Injury: Modified RIFLE Classification	
Stages	**Change in Serum Creatinine (up to 72 hours) compared to Baseline**
Stage 1	Increase in serum creatinine to 150-200% (1.5-2.0 x increase compared with baseline) or increase of ≥ 0.3 mg/dl (≥26.4 µmol/L)
Stage 2*	Increase in serum creatinine to 200-300% (> 2-3 x increase compared with baseline)
Stage 3*/**	Increase in serum creatinine to ≥300% (> 3 x increase compared with baseline) or serum creatinine of ≥ 4.0 mg/d (≥354 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L)
* Stage 2 and 3 acute renal injuries will be considered to be serious adverse events. ** Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria	

ACUTE VESSEL OCCLUSION

The state of complete luminal obstruction with no antegrade blood flow.

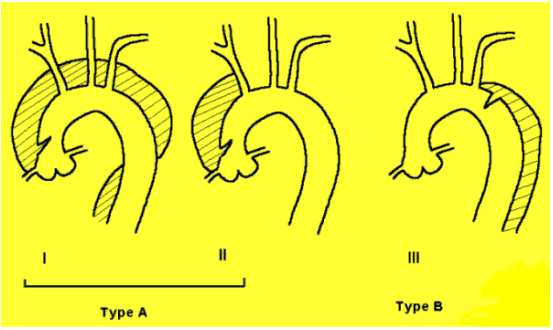
ADVERSE EVENT (AE)

An adverse event is any undesirable experience (sign, symptom, illness, or other medical event) occurring to the subject, and that appears or worsens during the clinical trial, whether or not associated with the investigational products or related procedures.

AORTIC DISSECTION

Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction. Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) as shown below.

- Major Aortic Dissection: Type A and Types I and II.
    - Major aortic dissections will be considered to be serious adverse events.
- Minor Aortic Dissection: Type B and Type III



AORTIC REGURGITATION (AR)

Aortic valve incompetence resulting in backward flow of blood**.**

Aortic Valve Regurgitation will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

Prosthetic Aortic Valve Regurgitation Criteria (Central and Paravalvular)			
Parameter	Mild	Moderate	Severe
Valve Structure and Motion Mechanical or bioprosethic	Usually normal	Usually abnormal	Usually abnormal
Structural parameters Left ventricular size	Normal	Normal/mildly dilated	Dilated
Doppler parameters (qualitative or semiquantitative) Jet width in central jets (% LVO diameter): color* Jet density: CW Doppler Jet deceleration rate (PHT, ms): CW Doppler** LV outflow vs. pulmonary flow: PW Doppler Diastolic flow reversal in the descending aorta: PW Doppler Circumferential extent of paraprosthetic AR (%)***	 Narrow (≤25%) Incomplete or faint Slow (<500) Slightly increased Absent or brief Early diastolic <10	 Intermediate (26-64%) Dense Variable (200-500) Intermediate Intermediate 10-20	 Large (≥65%) Dense Steep (<200) Greatly increased Prominent, Holodiastolic >20
Doppler parameters (quantitative) Regurgitant volume (mL/beat) Regurgitant fraction (%)	 <30 <30	 30-59 30-50	 >60 >50

*Parameter applicable to central jets and is less accurate in eccentric jets
** Influenced by left ventricular compliance
*** For paravalvular aortic regurgitation
AR=aortic regurgitation; CW= continuous wave; LVO= left ventricular outflow; PW= pulsed wave

Moderate or severe aortic regurgitation (AR) will be considered a serious adverse event.

AORTIC STENOSIS (AS)

A narrowing, stiffening or stricture of the aortic valve.

Aortic Stenosis of the native valve will be defined based on the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)

Aortic Stenosis			
Indicator	**Mild**	**Moderate**	**Severe**
Jet velocity (m/s)	Less than 3.0	3.0-4.0	Greater than 4.0
Mean gradient (mmHg)	Less than 25	25-40	Greater than 40
Valve area (cm^2)	Greater than 1.5	1.0-1.5	Less than 1.0
Valve area index (cm^2/m^2)			Less than 0.6

Aortic Stenosis of the prosthetic valve will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

Prosthetic Aortic Valve Stenosis Criteria[a]			
Parameter	**Normal**	**Possible stenosis**	**Significant stenosis**
Peak velocity (m/s)[b]	<3	3-4	>4
Mean gradient (mmHg) [b]	<20	20-35	>35
Doppler velocity index	≥0.30	0.29-0.25	<0.25
Effective orifice area (cm^2)	>1.2	1.2-0.8	<0.80
Contour of the jet velocity through the prosthetic valve	Triangular, early peaking	Triangular to intermediate	Rounded, symmetrical contour
Acceleration time (ms)	<80	80-100	>100

[a]In conditions of normal or near normal stroke volume (50-70 mL).

[b]These parameters are more affected by flow, including concomitant aortic regurgitation.

Moderate or severe AS will be considered a serious adverse event.

ARRHYTHMIA

Any variation from the normal rhythm of the heart beat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia.

- Major Arrhythmias: Complete heart block, ventricular tachycardia and ventricular fibrillation
- Serious Arrhythmias: Any arrhythmia requiring surgical or invasive intervention or DC cardioversion

BLEEDING EVENT

Bleeding event will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

Life-threatening or Disabling Bleeding
• Fatal bleeding OR • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome **OR** • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery **OR** • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units*
Major Bleeding
• Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2-3 units of whole blood/RBC **AND** • Does not meet criteria of life-threatening or disabling bleeding
Minor Bleeding
• Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling or major
* Given one *unit* of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.

Life-threatening and Major bleeding events are considered to be serious.

BUNDLE BRANCH BLOCK

ACC/AHA/HRS 2006 Key Data Elements and Definitions for Electrophysiological Studies and Procedures; A Report of the American College of Cardiology/ American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology), JACC, Vol. 48, No. 11, 2006.

Left Bundle Branch Block (LBBB)

- QRS duration 120 ms or longer
- Delayed onset of intrinsicoid deflection in 1, V5, and V6 _60 ms
- Broad and notched or slurred R waves in I, aVL, V5, and V6
- rS or QS complexes in right precordial leads
- ST-segment and T waves in opposite polarity to the major QRS deflection

Right Bundle Branch Block (RBBB)

- QRS duration _120 ms
- rsR= or rSR= complexes in V1 and V2
- Delayed onset of intrinsicoid deflection in V1 and V2 _50 ms
- Broad, slurred S wave in 1, V5,

Any new or worsening LBBB or RBBB that requires the placement of a permanent pacemaker and/or other surgical or invasive intervention will be considered to be serious.

CARDIAC TAMPONADE

Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.

CARDIOGENIC SHOCK

Patient was, at the time of procedure, in a clinical state of hypoperfusion sustained for greater than 30 minutes, according to either of the following criteria:
1. Systolic BP < 80 and/or Cardiac Index < 1.8 despite maximal treatment;
2. IV inotropes and/or IABP necessary to maintain Systolic BP > 80 and/or CI > 1.8

CEREBRAL INFARCTION

Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke, otherwise it is an asymptomatic cerebral infarction.

CHRONIC RENAL INSUFFICIENCY

Kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for or ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

CONDUCTION DISTURBANCE REQUIRING PERMANENT PACEMAKER IMPLANTATION

ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)
Any disturbance in the cardiac electrical conduction system that meets the American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Rhythm Society (HRS) Class I or IIa Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities for Acquired Atrioventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block.

DEATH

A serious adverse event that is classified by the following:

All-cause death: All deaths from any cause after a valve intervention. This includes all cardiovascular and non-cardiovascular deaths.

Cardiovascular Death:

(Cardiovascular death will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium". Any one of the following criteria:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

Note: All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac

.

Non-cardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Valve-related death:

- Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis;
- Death related to reintervention on the operated valve

DEVICE MIGRATION/VALVE EMBOLISM

Obvious spontaneous movement of the Medtronic CoreValve® PAV from its documented original implant position, after access site closure, as confirmed by X-ray, echocardiography, CT scan or direct assessment during open heart surgery or autopsy.

DEVICE MALPLACEMENT/MALPOSITION

Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery or procedure that necessitates placement in the non-therapeutic location. This does include movement during retrieval of the delivery catheter following BAV post implantation

DEVICE RELATED

Events that occur as the direct result of the Medtronic CoreValve® System (MCS) as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system components.

DEVICE RELATED COMPLICATIONS

Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.

DEVICE SUCCESS

Device success is defined as follows:

- successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,
- correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),
- Intended performance of the prosthetic valve[1] (aortic valve area > 1.2 cm^2 for 26, 29 and 31mm valves, ≥ 0.9 cm^2 for 23mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR)
- Only one valve implanted in the proper anatomical location

[1] assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge

EMBOLISM

Free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation that occurs in the absence of infection after the immediate perioperative period. *Embolism* may be manifested by a *neurological event* or a *noncerebral embolic event.*

ENCEPHALOPATHY

Guy M. McKhann, et al. Encephalopathy and Stroke After Coronary Artery Bypass Grafting Incidence, Consequences, and Prediction. Arch Neurol 2002;59:1422-1428.

Episodes of confusion, agitation and/or combativeness; alterations and fluctuations in levels of consciousness; acute problems with cognition, including memory and changes in perception including hallucinations

ENDOCARDITIS

Implanted valve endocarditis: Any infection involving an implanted valve. The diagnosis of *operated valvular endocarditis* is based on one of the following criteria:

- re-operation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies;
- autopsy findings of abscess, pus, or vegetation involving a replaced valve; or
- in the absence of reoperation or autopsy, meeting of the Duke Criteria for endocarditis.

Infective endocarditis is diagnosed based on Duke criteria and necessitates 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria

Major criteria 1: Positive blood culture for infective endocarditis

Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below:

- Viridans streptococci, *Streptococcus bovis*, or HACEK group (*Haemophilus*. *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis, Eikenella corrodens, Kingella* **or**
- Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus

-OR-

Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as:

- Two positive cultures of blood samples drawn >12 hours apart, or
- All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart)

Major criteria 2: Evidence of endocardial involvement

Positive echocardiogram for infective endocarditis defined as:

- oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
- abscess, or

- new partial dehiscence of prosthetic valve

-OR-

New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor criteria 1: Predisposition: predisposing heart condition or intravenous drug use

Minor criteria 2: Fever: temperature > 38.0° C (100.4° F)

Minor criteria 3: Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

Minor criteria 4: Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor

Minor criteria 5: Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis

Minor criteria 6: Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above

EXPLANT

Removal of the investigational valve implant for any reason, including post-mortem.

HEMOLYSIS

A plasma free hemoglobin value noted as clinically significant by the physician is considered to be hemolysis and a reportable adverse event.

- **Major hemolysis:** A plasma free hemoglobin value > 40 mg/dL that requires intervention (i.e. iron replacement, blood transfusion, folic acid administration, corticosteroids, Intravenous immunoglobulin G (IVIG) and/or surgery). Major hemolysis events will be considered to be serious adverse events.

- **Minor hemolysis:** A plasma free hemoglobin value > 40 mg/dL that does not require intervention.

HOSPITALIZATION FOR SIGNS AND SYMPTOMS RELATED TO AORTIC VALVE DISEASE

Aortic valve disease hospitalizations are defined as a non-elective hospital admission for signs and symptoms related to aortic valve disease (as described below) that results in at least a two-night stay (i.e., where the admission date and the discharge date differ by at least two calendar days). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. This does include the administration or augmentation of intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).
Patients with signs and symptoms related to aortic valve disease (as described below) who are hospitalized for less than two days or who are treated and released from the emergency department or an outpatient clinic (including treatment for intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators)), will not be counted as aortic valve disease hospitalizations.

Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms.

Signs and Symptoms of Aortic Valve Disease	
Sign/Symtpom	**Definition**
Aortic Valve Dysfunction	
Shortness of breath/dyspnea	A feeling of difficult or labored breathing that is out of proportion to the patient's level of physical activity
Exercise intolerance	A condition where the patient is unable to do physical exercise at the level or for the duration that would be expected of someone in his/her general physical condition, or experiences unusually severe post-exercise pain, fatigue,

	or other negative effects
Dizziness/syncope	Lightheadness or unsteadiness of gait or a partial or complete loss of consciousness with interruption of awareness of oneself and ones surroundings
Chest pain	Discomfort and soreness in and around the chest
Worsening Heart Failure	
Volume Overload	
Orthopnea	Dyspnea in which the person can breathe comfortably only when standing or sitting erect
Paroxysmal nocturnal dyspnea	Acute dyspnea caused by the lung congestion and edema that results from partial heart failure and occurring suddenly at night, usually an hour or two after the individual has fallen asleep.
Jugular venous distension	With the patient is positioned under 45°, and the filling level of the jugular vein determined. An abnormal response is more than 3 centimeters above the sternal angle.
Hepatomegaly	Palpation of the edge of the liver below the edge of the ribs without inspiration
Peripheral edema	Swelling of tissues, usually in the lower limbs, due to the accumulation of fluids.
Pulmonary rales	Small clicking, bubbling, or rattling sounds in the lung associated with inspiration
Abdominal-jugular reflux	An elevation of venous pressure visible in the jugular veins and measurable in the veins of the arm, produced in active or impending congestive heart failure by firm pressure with the flat hand over the abdomen.
Radiographic evidence of pulmonary edema	NA
Elevated B-type natriuretic peptide level	NA
Hypoperfusion	
Narrow pulse pressure	Pulse pressure < 30 mmHg
Hypotension	Systolic BP < 90 systolic
Renal or hepatic dysfunction	• Rise in baseline creatinine by 25% • Increase in LFT (SGOT, SGPT) > 2 times normal
Low serum sodium concentration	Serum sodium < 130 mEq/dL

INFECTION

Elevated body temperature (fever), and White Blood Count (WBC) > 12,000/ml, and Significant leftward shift on Differential.

INTRACRANIAL HEMORRHAGE

Collection of blood between the brain and skull. Subcategorized as epidural, subdural and subrachnoid bleeds.

MAJOR ADVERSE CARDIOVASCULAR AND CEREBROVASCULAR EVENTS (MACCE)

Defined as a composite rate of

- all-cause death
- myocardial infarction (MI)
- all stroke, and
- reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

MAJOR ADVERSE EVENT (MAE)

Major Adverse events include the following:

- MACCE
- Acute kidney Injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Life-threatening, disabling or major bleeding
- Major vascular complication
- Cardiac Perforation
- Device Migration/Valve embolism

MITRAL STENOSIS

A narrowing, stiffening or stricture of the mitral valve.

ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)

Mitral Stenosis			
	Mild	**Moderate**	**Severe**
Mean Gradient (mmHg)	Less than 5	5-10	Greater than 10
Pulmonary artery systolic pressure (mmHg)	Less than 30	30-50	Greater than 50
Valve area (cm^2)	Greater than 1.5	1.0-1.5	Less than 1.0

Moderate or severe MS will be considered a serious adverse event.

MYOCARDIAL INFARCTION (MI)

Myocardial infarction will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

Peri-Procedural MI **(≤ 72 hours after the index procedure)**
1. New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality)
2. Elevated cardiac biomarkers (preferably CK-MB) within 72 hours after the index procedure, consisting of two or more post-procedure samples that are ≥ 6-8 hours

apart with a 20% increase in the second sample and a peak value exceeding 10x the 99th percentile upper reference limit (URL) **or** a peak value exceeding 5x the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads.

MYOCARDIAL INFARCTION (MI) - continued

Spontaneous MI **(> 72 hours after the index procedure)**
Any one of the following criteria: 1. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following: • ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]); • New pathological Q waves in at least 2 contiguous leads; • Imaging evidence of new loss of viable myocardium or new wall motion abnormality 2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. 3. Pathological findings of an acute myocardial infarction.

All myocardial infarctions will be considered serious adverse events.

NEUROLOGICAL EVENT

Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)

Classification system for defining cardiac disease and related functional limitations into four broad categorizations:

Class I	Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

PARAVALVULAR AORTIC REGURGITATION

Leakage due to a separation of the prosthetic valve from the annulus. Diagnosis of paravalvular leak may be obtained from echocardiogram; however definitive diagnosis is obtained at reoperation, explant, or autopsy.

All moderate or severe paravalvular leaks will be classified as Serious Adverse Events.

(Refer to the definition of Aortic Regurgitation for additional paravalvular leak severity criteria)

PATIENT PROSTHESIS MISMATCH (PPM)

Patient Prosthesis Mismatch will be defined according to the definition from Urso et al, Interact Cardiovasc Thorac Surg. 2009 Sep; 9(3):510-8. Epub 2009 Jun 4.

- Severe PPM will be defined as an EOA ≤ 0.65 cm2 /m2 BSA
- Moderate PPM defined as a patient with an EOA ≤ 0.85 cm2 /m2 BSA

PERMANENT PACEMAKER IMPLANTATION

Implantation of permanent pacemaker after the index procedure due to occurrence of conduction disturbances.

- **Procedure-related**: Permanent Pacemaker is implanted in subjects with new onset conduction disturbances or worsening of existing conduction disturbances
- **Not related to procedure**: Permanent Pacemaker is implanted in subjects with known conduction disturbances that did not advance after the index procedure.

PROCEDURE RELATED COMPLICATIONS

Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate patient selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.

PROCEDURAL SUCCESS

Defined as device success without occurrence of in-hospital MACCE.

PROCEDURE-RELATED EVENTS

Events occurring during or as a direct result of the index procedure. Events that occur before extubation and before access site closure are classified as procedural.

PROSTHETIC VALVE DYSFUNCTION

Prosthetic Valve Dysfunction will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium". Failure modes of prosthetic valve dysfunction include, but are not limited to, the following:

- Aortic Stenosis
    - Stent creep
    - Pannus
    - Calcification
    - Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardi-pulmonary resuscitation, blunt chest trauma)
    - Mal-sizing (prosthesis-patient mismatch(PPM))
    - Endocarditis
    - Prosthetic valve thrombosis
    - Native leaflet prolapse impeding prosthetic leaflet motion
- Aortic Regurgitation
    - Pannus
    - Calcification
    - Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardi-pulmonary resuscitation, blunt chest trauma)
    - Endocarditis
    - Prosthetic valve thrombosis

- Mal-position (too high, too low)/malplacement
- Acute mal-coaptation
- Leaflet wear, tear/perforation, prolapse or retraction
- Suture breakage or disruption
- Native leaflet prolapse impeding prosthetic leaflet motion

Prosthetic valve dysfunction will be considered serious when it meets the definition of a serious adverse event (SAE).

REINTERVENTION

Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical reoperations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered *reinterventions.* Reintervention is further subdivided into *surgical* and *percutaneous*.

RESPIRATORY INSUFFICIENCY

Post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio [FEV1/FVC] less than 70%.

Post-bronchodilator FEV1 less than 80% predicted, with or without chronic symptoms (i.e., cough or sputum production).

RESPIRATORY FAILURE

The need for ventilatory support for > 72 hours associated with an inability to wean from the respirator for any reason.

RIGHT VENTRICULAR INSUFFICIENCY

Defined as sequelae of right ventricular failure including the following:

- Significantly decreased right ventricular systolic and/or diastolic function
- Tricuspid valvular regurgitation secondary to elevated pressure

Clinical symptoms to include:

- Hepatic congestion
- Ascites
- Anasarca
- Presence of “hepato-jugular reflux”
- Edema

SERIOUS ADVERSE EVENT (SAE)

A serious adverse event (SAE) is an event that meets any of the following criteria:

- Results in subject death
- Is life threatening* (i.e., the subject was at risk of death at the time of the event)
- Results in inpatient hospitalization
- Results in prolonged existing hospitalization
- Results in persistent or significant disability**/incapacity
- Results in congenital anomaly/birth defect
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

*A life-threatening adverse event is any adverse event that places the subject, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

**The definition of disability is a substantial disruption of a person's ability to conduct normal life functions.

STROKE (CVA)

Stroke and TIA will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

Stroke Diagnostic Criteria

• Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
• Duration of a focal or global neurological deficit ≥ 24 hours; OR < 24 hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death
• No other readily identifiable non-stroke cause for the clinical presentations (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*
• Confirmation of the diagnosis by at least one of the following:
  ○ Neurology or neurosurgical specialist
  ○ Neuroimaging procedure (MR or CT scan or cerebral angiography)
  ○ Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

Stroke Definitions

• Transient Ischemic Attack
  ○ New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
  ○ Neuroimaging without tissue injury
• Stroke: (diagnosis as above, preferably with positive neuroimaging study)+
  ○ Minor (non-clinically important disability) - modified Rankin score < 2 at 30 and 90 days
  ○ Major (clinically important disability) - modified Rankin score ≥ 2 at 30 and 90 days

*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies

+ Major and Minor stroke will be adjudicated and analyzed using the MRS at 90 days only.

Modified Rankin Scale

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Clinically important disabilities (major strokes) will be considered to be serious adverse events.

Strokes will be further categorized to the following:

- Ischemic stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

TECHNICAL OBSERVATION

A defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent.

TRANSIENT ISCHEMIC ATTACK (TIA)

(Refer to the definition of TIA under stroke above.)

- New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
- Neuroimaging without tissue injury

VALVE THROMBOSIS

Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valve thrombus found at autopsy in a subject whose cause of death was not valve-related or found at operation for an unrelated indication should also be counted as *valve thrombosis.*

VASCULAR COMPLICATIONS

Vascular Complications will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

Vascular Access Site and Access Related Complications
Major Vascular Complications
1. Any thoracic aortic dissection 2. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥ 4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g. hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurologic impairment) 3. Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage
Minor Vascular Complications
1. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula or pseudoaneuysms requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥ 2 but < 4 units) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage 2. Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage 3. Failure of percutaneous access site closure resulting in interventional (e.g. stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥4 units), or irreversible end-organ damage

Major vascular complications will be considered to be serious adverse events.

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